An INTRODUCTION
to MEDICAL MYCOLOGY

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GEORGE M. LEWIS, M.D.

MARY E. HOPPER, M.S.

J. WALTER WILSON, M.D.

ORDA A. PLUNKETT, Ph.D.

Published at

200 EAST ILLINOIS STREET • CHICAGO

to

MEDICAL MYCOLOGY

Professor of Clinical Medicine (Dermatology), Cornell University Medical College
Attending Physician (Dermatology), The New York Hospital

Research Fellow in Medicine, Cornell University Medical College

Clinical Professor of Medicine, University of Southern California
Attending Dermatologist, Los Angeles County Hospital

Professor of Botany, University of California at Los Angeles
Consultant in Mycology, Los Angeles County Hospital

FOURTH EDITION

by

THE YEAR BOOK PUBLISHERS • INC.

Second Edition, 1943
Third Edition, 1948
Fourth Edition, 1958

PRINTED IN THE U S A

Preface to the Fourth Edition

MEDICAL mycology as an important science has come of age. Chief credit for current progress should be given to the few, but active, qualified mycologists engaged full time in research and in teaching. The contributions made by these dedicated scientists have been fundamental and significant. Hope for the future would seem to depend in large measure on the continued exploration of basic fields. Nevertheless, we should not overlook or disparage in any way the quite valuable participation by clinicians and by part-time workers There is still an opportunity in this field for all who wish to work.

Medical mycology is of considerable practical interest, since diseases caused by fungi, or in which fungi may be suspected as etiologic, constitute a sizable percentage of the disorders affecting the skin, and to a lesser degree other organs of the body Dermatologists thus have a particular interest in medical mycology, but it is also desirable for specialists in other fields, as well as general practitioners, to become familiar with the clinical features of mycotic diseases, to learn at least the rudiments of appropriate laboratory procedures, and to base their therapeutic attack on knowledge of the currently

The mycolog
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be utilized The
ing appropriate specimens and interpreting them correctly. It is often difficult to secure the services of a person who has acquired specialized knowledge in the field, preferably following university education with emphasis on the sciences Such a person ideally should have experience in basic and fundamental mycology, followed by more specialized work with the dermatophytes, the yeast-like fungi and other fungi of potential or obligatory invasive characteristics. Prior experience in bacteriology is helpful, since many of the technical procedures employed in the mycology laboratory are similar to those used by the bacteriologist In many smaller

institutions, the mycology specimens are processed in the bacteriology laboratory and interpreted by a bacteriologist. This is seldom completely satisfactory.

The private laboratory in connection with a physician's office is useful in helping to establish precise diagnoses and to carry out routine procedures. As a rule, there are limitations, and if a cultural growth of unusual appearance is isolated, it may require help from an "expert" However, the making of direct mounts, cultures of common pathogens, Wood's light examinations and trichophytin tests are all within the abilities and training of most dermatologists. For many, the subject is so interesting as to constitute a medical hobby.

The first edition of this book was published 18 years ago. Two subsequent editions, in 1943 and in 1948, apparently satisfied, in part at least, the need for a practical treatise on fungous diseases Supplies of the third edition were exhausted more than four years ago. To prepare this present volume required almost complete rewriting in order to cull out obsolete portions and parts in which emphasis appeared to have been overstressed, and, of even more importance, to try to summarize and incorporate the many advances in knowledge. Fortunately, I was able to persuade Dr. J Walter Wilson and Dr Orda A. Plunkett to collaborate with Miss Hopper and myself. This proved to be most constructive. I am confident that readers of this text will appreciate the thought and effort which Drs. Wilson and Plunkett devoted to their contributions. Dr. Wilson rewrote the chapters on the deep mycoses and Dr. Plunkett wrote the chapter on contaminants Miss Hopper worked on technical phases and also is responsible for most of the pictures, either new or freshly prepared The collaboration was not rigidly defined, and included critical reading of all chapters by all four authors Consequently, this book must be considered a joint effort

A major change has been made in the format. In previous editions the clinical aspects of the mycoses were considered first and the laboratory technics and characteristics of the pathogenic fungi were detailed in subsequent chapters In this edition the clinical and laboratory phases are not separated, and each of the various pathogenic fungi are so considered Furthermore, a beginning has been made to abandon some time-honored clinical designations as no longer valid, in favor of an etiologic approach, believing that this is the ultimate goal in the understanding and in the description of disease processes Perhaps it will not be too long before terms such as dermatophytosis, tinea capitis, tinea circinata and tinea barbae are discarded, although habits are difficult to change Retention of these clinical appellations of nonexistent syndromes is a definite handicap to progress

We are indebted to many friends and colleagues who have offered valuable advice or who have generously donated photographs While specific acknowledgments are made in the legends under the illustrations, I should like particularly to thank Dr. Lewis Pipkin, whose unselfish, wholehearted and enthusiastic interest in medical mycology is a great inspiration to his

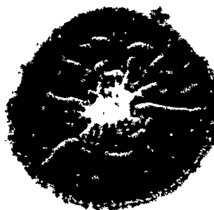
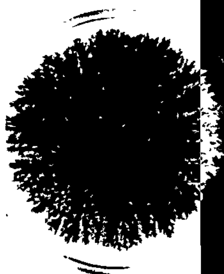
many friends. I should like also to acknowledge the invaluable assistance of Dr. Arturo C [illegible] ho wrote the chapter or [illegible] for this chapter. We fe [illegible] Desai of Bombay, India, supplied us with authoritative material in the preparation of the chapter on rhinosporidiosis. It is also a pleasurable duty to here record my gratitude for the constructive and selfless efforts of Mary Ellen Hopper. Without her talents, energy and patience, this text would never have materialized.

It has been a pleasant experience to work with The Year Book Publishers, who have been most courteous and understanding in our mutual desire to create a useful text in a finely printed volume.

—George M. Lewis

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These are inherent ferrugineum upper nt, lower right, Trichophyton violaceum

1. The Superficial Mycoses

PROGRESS in the understanding of the superficial fungous diseases has stemmed in large part from a careful delineation of the manifestations of the various dermatophytes, but common usage has so far dictated the retention of terms which refer to a certain region or structure of the body. The retention of a term such as tinea barbae as the name of a disease is hard to defend, since the beard, while it may be the most prominent site, is often not the sole location. In a child, the scalp may be favored by the same species of fungus. A fungous disease of the beard may be caused by one of several fungi. Similar objections are valid for tinea capitis, tinea corporis, dermatophytosis, tinea cruris, and onychomycosis There is of course some value in not discarding too abruptly this traditional approach. It is convenient to use a clinical term, as an impression, before laboratory work has been undertaken, especially when there may be difficulty in differential diagnosis from nonmycotic disorders. The graduate student beginning his dermatologic career may not be familiar with the potentialities of the various dermatophytes. Furthermore, all dermatologic textbooks use these old-fashioned expressions With the development of his powers of careful observation and increase in factual knowledge, the serious student will develop the ability to think etiologically of the superficial mycoses, just as he does of the deep mycoses and other diseases of which the cause is known. It would seem that this is sound practice. Specific diagnostic methods in mycology are simple and have been mastered by all trained dermatologists taking the examination of the American Board of Dermatology There are not many dermatologic clinics or private offices in which facilities for a direct mount, culture, trichophytin test, and Wood light examination are not available The practical effect of the etiologic approach is to place the subject on a higher plane, since a patient is given a specific diagnosis, likely associated lesions are searched for, the prognosis can be estimated more exactly, and treatment often can be outlined with confidence

- **I. MICROSPORUMS**
  - Microsporums purs de type humain
    - *Microsporum Audouini* (¹)
    - M. umbonatum
    - M. tardum
    - M. velveticum
  - Microsporums ou d'origine animale, conservant longtemps leur type parasitaire jeune
    - Microsporum *lanosum*
    - M. felineum
    - M. equinum
    - M. fulvum
    - M. villosum
    - M. pubescens
    - M. tomentosum
- **II. TRICHOPHYTONS**
  - ENDOTHRIX
    - ENDOTHRIX PURS
      - Espèces types fréquentes
        - Trichophyton *crateriforme*
        - Tr. *acuminatum*
        - Tr. *violaceum*
      - Espèces rares ou étrangères
        - Tr. effractum
        - Tr. fumatum (²)
        - Tr. umbilicatum
        - Tr. regulare
        - Tr. *sulfureum*
        - Tr. polygonum
        - Tr. exsiccatum
        - Tr. circonvolutum
        - Tr. pilosum
        - Tr. glabrum
    - NÉO-ENDOTHRIX
      - Conservant le type parasitaire de la période jeune
        - Trichophyton *cerebriforme*
        - Tr. plicatile
  - ECTOTHRIX
    - MICROÏDES
      - Type *gypseum*
        - Trichophyton *asteroides*
        - Tr. radiolatum
        - Tr. lacticolor
        - Tr. granulosum
        - Tr. farinulentum
        - Tr. persicolor
      - Type *niveum*
        - Trichophyton *radians*
        - Tr. denticulatum
    - MÉGASPORES
      - A culture *rosacée*
        - Tr. *rosaceum*
        - Tr. vinosum
        - Tr. *equinum*
        - Trichophyton caninum
      - A culture *faviforme*
        - Trichophyton *ochraceum*
        - Tr. album
        - Tr. discoides
- **III. ACHORIONS**
  - Achorion du favus humain
    - *Achorion Schoenleini*
  - Achorions animaux
    - A. Quinckeanum
    - A. gallinae
    - A. gypseum
    - Oospora canina

(¹) Les espèces les plus importantes ont leur nom en italique.

(²) A côté du *Trichophyton fumatum*, et en tout cas parmi les Trichophytons endothrix il faudra bientôt faire place à deux nouvelles espèces isolées à Venise dans le service de M. le Prof. Fiocco par le Dr Minassian. L'une, *Trichophyton sulfureum*, à culture cérébriforme, poudreuse et crayeuse, présente en son centre une boursouflure blanchâtre difforme caractéristique sur milieu d'épreuve. L'autre, *Trichophyton spongoides*, présente une boursouflure centrale analogue mais de couleur bistre, neutre, non poudreuse et semblable à une éponge brune déposée sur une aréole poudreuse et crayeuse.

Fig. 1. Sabouraud's classification of ringworm fungi. (*Reproduced from Les Teignes, Paris, Masson & Cie, 1910.*)

The following discussion and the accompanying tables are incomplete and intended only to provide some readily available differential-diagnostic data to help direct the reader to specific sections.

TINEA CAPITIS

The patients are mainly but not exclusively children. The degree of inflammatory reaction varies from mild scaling to boggy, painful swellings (kerion). There is usually loss of hair (spontaneous epilation) if the inflammation is severe or breaking off of hair at or near the surface of the scalp in other cases The tendency is toward development of patchy areas in which the majority of the hair follicles are involved

TABLE 1 —DIAGNOSTIC FEATURES OF VARIETIES OF TINEA CAPITIS

Fungus	Inflammation	Wood Light	Incidence in U S A	Duration,* Weeks	Characteristics
M audouini	±	+	Common, urban	4–8	Gray patch
M canis	+++	+	Common	2–4	Inflammatory
M gypseum	++++	±	Rare	1–3	Solitary lesion, kerion
T. ferrugineum	–	–	Rare	8 +	In Orientals
T tonsurans	±	–	Chiefly in Southwest	2–8	Variable
T violaceum	±	+	Rare	8 +	Black dot
T schoenleini	±	+	Rare	8 +	Crusts, odor
T mentagrophytes	+++	–	Chiefly in country	1–3	Kerion

* Before treatment

In the table on tinea capitis (Table 1) the duration is approximate and refers to the time between onset and the first visit to a physician The exact time of onset is seldom known However, the figures given are indicative. Thus, if there is a history of more than five weeks' duration, the infection is due more likely to Microsporum audouini than to Microsporum canis. The characteristics mentioned usually apply, with many exceptions, as the reader will discover as he studies the specific disorder. The differentiation of tinea capitis from nonmycotic diseases is discussed in Chapter 2. The Wood light is a valuable aid, and when the findings are positive is confirmatory It should be kept in mind, however, that not all types of tinea capitis are characterized by fluorescence, so that a negative reaction does not rule out fungous disease The fluorescence of fungi and that observed after applications of grease or chemicals must be carefully distinguished.

TINEA BARBAE

The male beard may be infected by several fungi, as noted in Table 2. The clinical features vary considerably, depending on the infecting microorganism. Most of the highly inflammatory cases are observed in rural communities and are due either to Trichophyton mentagrophytes or to Trichophyton verrucosum. The response to follicular invasion of Trichophyton rubrum is so passive that the infection may be overlooked

TABLE 2 —CHARACTERISTICS OF TINEA BARBAE BASED ON ETIOLOGY

FUNGUS	INFLAMMATION	WOOD LIGHT	LESIONS ELSEWHERE	DURATION*, WEEKS	VECTOR
M canis	++	+	Body?	2–4	Pet
T mentagrophytes	++++	–	No	1–3	Horse, cow
T violaceum	+	+	No	8 +	Human
T rubrum	+	–	Feet, body	8 +	Self
T verrucosum	++++	–	Scalp, body	1–3	Cattle

* Before treatment

The differential diagnosis is chiefly from sycosis barbae. A simple test is often helpful. Traction on a hair on which a pyogenic coccus is the etiologic microorganism reveals difficulty in extracting and results in pain. In a fungous infection, the affected hair usually comes out readily and without pain. Follicular lesions occasionally appear in the beard as a reaction to an ingested drug, with iodides and bromides particularly to be suspected.

TINEA CORPORIS (TINEA CIRCINATA)

Tinea corporis refers to tinea of the nonhairy, nonintertriginous areas The classic appearance is that of a circinate lesion spreading peripherally, with a clearing center and an active, often vesicular, border. New lesions soon develop Children are more susceptible than adults Many other clinical types are observed, including ill-defined, branny scaling with little acute inflammation, solid plaques without any clearing in the center, configurate and gyrate lesions, and groups of vesicles. The commonest cause is M canis Finding this fungus should always direct attention to the scalp, to other children, and to the possibility that the infection was acquired from a pet If T rubrum is the cause of the condition, the feet and nails may well be a reservoir from which lesions on the glabrous skin developed Eczematization is often a feature of the inflammatory mycoses and may mask the underlying and more important component. At times it is a primary manifestation revealing a severe tissue reaction, but more commonly it is caused by ill-advised overtreatment

TABLE 3 — SOME CLINICAL FEATURES OF TINEA CORPORIS

Fungus	Inflammation	Circinate	Scaly	Crusted	Solid Plaque	Conglomerate	Granulomatous
M canis	+++	+		+			±
M audouini	+	+					
T schoenleini	+		+	+			
T. violaceum	±		+				
T mentagrophytes	++++	+		+			+
T. rubrum	+	+	+		+	+	±
T. verrucosum	++					+	

The various expressions of superficial fungous disease affecting the smooth skin are often simulated by diseases of many diverse etiologies Differentiation of such diseases as pityriasis rosea (particularly the initial herald patch), psoriasis, parapsoriasis, seborrheic dermatitis, dermatitis medicamentosa, and nummular eczema may require careful clinical observation and laboratory investigation. Rarely, diseases such as dermatitis herpetiformis may come under suspicion.

DERMATOPHYTOSIS (DERMATOMYCOSIS)

The term dermatophytosis is usually restricted to superficial fungous infections of the feet, hands, and nails, although spread to adjacent or remote areas may be included When the feet are involved in an inflamma-

TABLE 4 — SOME FEATURES OF THE THREE COMMON VARIETIES OF DERMATOPHYTOSIS

Fungus	Type	Chief Location	Dermatophytid	Trichophytin Reaction	Prognosis	Treatment
T mentagrophytes	Acute	Interdigital web	+	Positive; tuberculin like	Good	Mild
T rubrum	Chronic	Sole, nails	—	Positive; immediate wheal	Poor	Strong
E floccosum	Subacute	Groin	—	Negative or weakly positive	Excellent	Medium

tory fungous infection, allergic vesicular lesions may develop on the sides of the fingers or on the palms or occasionally elsewhere.

As with the other terms based on distribution of the visible lesions, this title refers to more than one disease At least three distinct syndromes may develop under the aegis of this term Once the etiologic agent has been

determined or even suspected from the clinical features, the term dermatophytosis becomes meaningless. In such cases it is appropriate to discard the term. For minimal expressions, such as interdigital scaling or maceration, the term dermatophytosis or, better, tinea pedis might be used temporarily while one is awaiting the result of the culture. The differential diagnosis of dermatophytosis is discussed under the more specific titles of trichophytosis (T. mentagrophytes); trichophytosis (T. rubrum), and epidermophytosis (Epidermophyton floccosum).

In differential diagnosis the chief difficulty lies with the inflammatory eruptions of the feet and hands. There is still a widely held erroneous belief that all foot disorders are of mycotic origin. Careful clinical study and laboratory investigation will fail to confirm this. The list of inflammatory disorders commonly found on the feet is large and impressive. Pyogenic microorganisms, often in connection with hyperhidrosis, are frequent offenders. Pustular psoriasis and psoriasis may not be recognized. Localized atopic dermatitis (neurodermatitis) selects the feet or hands or both as a not uncommon locale However, the chief source of error is in overlooking contact dermatitis Since the feet and hands are subject to considerable traumatic and chemical irritation as well as to exposure to a wide variety of sensitizing materials, the presence of eczematous eruptions due to such exposure is remarkably common.

TINEA CRURIS

The lesions of tinea cruris are classically bilateral and frequently symmetric The upper, inner thighs are the usual sites, but spread often occurs to the intergluteal sections and to the scrotum. The eruption is usually diffuse, scaly, and sharply marginated. In most instances, the causal fungus is E floccosum One should remember that the feet are frequently affected T rubrum may also be a cause, in which case the eruption is usually unilateral.

ONYCHOMYCOSIS

As noted in Table 5, it is often possible to distinguish, clinically, features pointing etiologically to a particular species of fungus If the patient has a solitary fingernail involved, is a middle-aged woman whose work includes frequent contact with soapy water, and has an associated paronychia, the cause is more than likely to be Candida albicans This impression is strengthened if on clinical examination the affected nail shows lateral striping and irregularity of the nail plate but no friability or lack of luster The majority of nail infections which reveal no visible associated inflammation and in which the findings are yellow color, friability, and opacity are found on culture to be caused by T rubrum There is a tendency for insidious spread from toenails to fingernails, and eventually many nails

TABLE 5.—ONYCHOMYCOSIS

Fungus	Age	Onset	Number of Nails	Paronychia	Friability	Other Sites
T rubrum	Any	Free margin	1–20	–	+++	Soles
T. mentagrophytes	20–30	Surface (toe) Base (finger)	1	+ –	–	Interdigits (feet)
C. albicans	40 +	Base, edges	1–2	+++	–	Gastrointestinal tract, interdigits

may be involved. In T. mentagrophytes infection of the toenail, there may be an acute reaction with inflammation involving the nail bed, which may cause separation of the nail and spontaneous cure. This fungus may also colonize on the surface of a nail (so-called leukonychia trichophytica) and form a white mat, which may be readily scraped off. Solitary fingernail infections of acute inflammatory type may follow a visit to a beauty parlor for a manicure. The pattern is not so definitive for infections caused by other pathogenic fungi or for the occasional nail disorders apparently caused by a saprophyte or in which a saprophyte is isolated. In some of the latter cases further search for pathogenic fungi would be rewarding

SUMMARY

This chapter is in effect an introduction to the superficial fungous infections. The reader is referred to the following chapters for particular information The disease syndromes of the superficial fungi are usually well delineated, and one is rarely justified in being content with a clinical diagnosis based on the presence of symptoms in a particular part of the body. It is more rewarding to think etiologically.

2. Microsporosis
(Microsporum audouini)

MICROSPOROSIS (Microsporum audouini) is the prototype of the epidemic or sporadic affliction known as ringworm of the scalp (tinea capitis). Occasionally the glabrous skin may be affected (tinea corporis)

ETIOLOGY

M. audouini is of world-wide distribution and particularly favors large cities Epidemics of tinea capitis in schools, foundling homes, and other institutions are usually caused by this fungus. Children before the age of puberty are particularly susceptible Our highest incidence occurred at age 8 and at a somewhat younger age in Negro children Bereston and Robinson recorded a scalp infection in an infant 4 weeks old Boys are much more commonly affected than girls, the ratio in our experience being 3:1. However, observers record wide variations. For instance, Crocker stated that in 600 cases the disease was 6 per cent more prevalent in boys, while Beeson noted that 85 per cent of his patients were boys It is therefore probable that local conditions and customs, as well as the social status of the patients (most of the patients are from the lower economic strata), may affect the incidence. It has been widely held that the shorter hair of boys and their more vigorous physical play are important factors resulting in a higher incidence of infection Rothman postulated that adult sebum is more abundant and more fungistatic than that of children and that this is the reason why adults are less likely to acquire tinea capitis Kligman was unable to verify Rothman's conclusions, finding no difference in the fungistatic action of the two types of sebum

EPIDEMIOLOGY

The disease is commonly transmitted by contact from child to child We have isolated M audouini from combs, caps, and infected hairs found

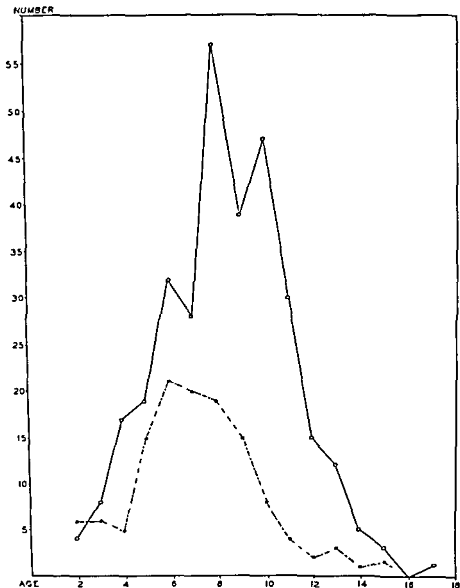


Fig 2. Age incidence of 444 children with tinea capitis due to Microsporum audouini Solid line represents 317 white children, broken line, 127 Negro children

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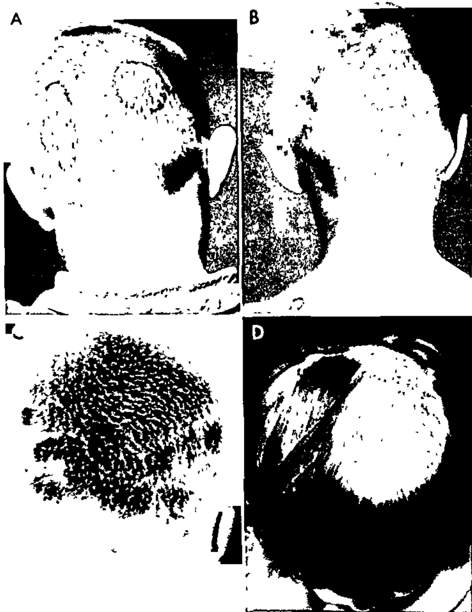


Fig 3 Microsporosis (M audouini) There is often only slight evidence of inflamma-

on theater seats and on other inanimate objects. From 1943 to 1947 there occurred in New York an increase in the number of cases of infection approximating epidemic proportions. The experience in New York City, where thousands of cases of tinea capitis swamped available facilities, has since been duplicated in most large and medium-sized cities of the United States. This was the first time that such a problem had been encountered, although both before and after the mid-forties the disease had had a limited incidence in all large centers of population in the United States. Even during the height of the epidemic, it was notable that not all children who were exposed acquired the disease In a few recorded studies of epidemics in schools, only from 5 to 20 per cent of the children were infected This observation would presuppose that there is a considerable variation in natural susceptibility or that infection requires a special breakdown in resistance, such as trauma Kligman carried out experimental studies on the scalps of children in an institution for mental defectives An epidemic had been in progress in the institution for a year, and 5 per cent of the inmates had been naturally infected He found that trauma was required prior to inoculation and that naturally infected hair was more reliable as an inoculum than cultural material. Of children 61 per cent and of adults 44 per cent could be infected with M audouini. It is probable, therefore, that the termination of an epidemic is due in main to exhaustion of the susceptible individuals in a community or school rather than to any decrease in virulence of the fungus or promptness of cure by roentgen rays.

CLINICAL CHARACTERISTICS

As a rule the invasion of M audouini results in minimal inflammatory reaction The scalp is usually involved (tinea capitis) This fungus is responsible for the classic type of scalp ringworm known as the "gray patch." The onset is usually insidious, and the duration of the infection averages over eight months When the condition is first detected by the parent, guardian, or teacher, there are one or several small areas in which the hair is dull, discolored, and broken off Club, or resting, hairs may be found scattered in a patch or at the edge, and these show limited or no infection. The surface of the patch is scaly The patch enlarges peripherally and retains its circinate shape As a rule little redness is noted, but occasionally a considerable degree of inflammation is present. Development of kerion is rare We have observed that the infection frequently begins along the part of the hair or where the hair is short When first examined, the lesions are usually in the occipital and temporal regions Often a number of lesions spread peripherally, finally becoming as large as a silver dollar or larger The total percentage of involvement rarely exceeds one-third of the available scalp surface It is not unusual for solitary follicular infections to occur without surface infection In such instances there is little or no tendency to spread to contiguous or remote sites In the cases observed in

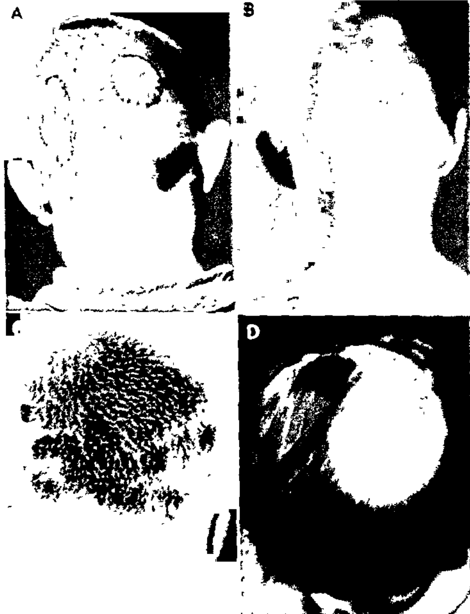


Fig 3. Microsporosis (M oudouini). There [illegible] tion A, two obscure lesions in occipital region [illegible] hairs B, circinate lesions on scalp and left [illegible] C, [illegible] pecia, involved hairs being broken off and mostly [illegible] D, [illegible] in case in which treatment was neglected

on theater seats and on other inanimate objects. From 1943 to 1947 there occurred in New York an increase in the number of cases of infection approximating epidemic proportions The experience in New York City, where thousands of cases of tinea capitis swamped available facilities, has since been duplicated in most large and medium-sized cities of the United States This was the first time that such a problem had been encountered, although both before and after the mid-forties the disease had had a limited incidence in all large centers of population in the United States. Even during the height of the epidemic, it was notable that not all children who were exposed acquired the disease In a few recorded studies of epidemics in schools, only from 5 to 20 per cent of the children were infected. This observation would presuppose that there is a considerable variation in natural susceptibility or that infection requires a special breakdown in resistance, such as trauma. Kligman carried out experimental studies on the scalps of children in an institution for mental defectives. An epidemic had been in progress in the institution for a year, and 5 per cent of the inmates had been naturally infected He found that trauma was required prior to inoculation and that naturally infected hair was more reliable as an inoculum than cultural material. Of children 61 per cent and of adults 44 per cent could be infected with M. audouini. It is probable, therefore, that the termination of an epidemic is due in main to exhaustion of the susceptible individuals in a community or school rather than to any decrease in virulence of the fungus or promptness of cure by roentgen rays.

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As a rule the invasion of M audouini results in minimal inflammatory reaction The scalp is usually involved (tinea capitis). This fungus is responsible for the classic type of scalp ringworm known as the "gray patch" The onset is usually insidious, and the duration of the infection averages over eight months When the condition is first detected by the parent, guardian, or teacher, there are one or several small areas in which the hair is dull, discolored, and broken off. Club, or resting, hairs may be found scattered in a patch or at the edge, and these show limited or no infection. The surface of the patch is scaly The patch enlarges peripherally and retains its circinate shape. As a rule little redness is noted, but occasionally a considerable degree of inflammation is present Development of kerion is rare We have observed that the infection frequently begins along the part of the hair or where the hair is short When first examined, the lesions are usually in the occipital and temporal regions Often a number of lesions spread peripherally, finally becoming as large as a silver dollar or larger. The total percentage of involvement rarely exceeds one-third of the available scalp surface It is not unusual for solitary follicular infections to occur without surface infection In such instances there is little or no tendency to spread to contiguous or remote sites In the cases observed in

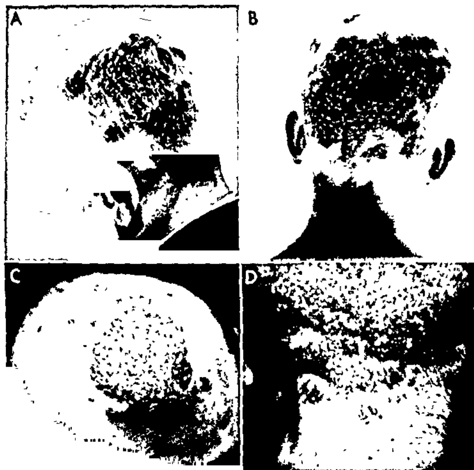


Fig. 4 Microsporosis (M. audouini). Severe inflammation is exception but may occur after X-ray therapy or spontaneously A, prior to roentgen therapy, disease manifested as gray-patch, scaly plaques B, three weeks after roentgen therapy, with severe inflammatory pustular eruption. Erythematous papular lesions were noted on trunk and ex-

New York during the epidemic of 1943 to 1947, there was a tendency for the infection to localize to the occipital region. The lesions were more frequently inflammatory than in the ordinary sporadic disease, and associated lesions on the glabrous skin were more commonly observed. Montgomery and Walzer reported a case of infection of the eyelashes in a patient with tinea capitis. The case of a 17-year-old girl with involvement of the pubic hair and glabrous skin of the lower abdomen was reported by Franks and Taschdjian.

The glabrous skin is affected occasionally (tinea corporis) and may be involved primarily or secondarily from the scalp disease. It is sometimes observed in mothers of patients. The degree of inflammation is usually slight and may be overlooked unless the physician is alert. It is good practice to observe carefully the adjacent skin of patients with tinea capitis and to examine all the contacts, including other children and adults. The clinical lesion is usually a circinate scaly plaque with clearing center. There is peripheral enlargement and, eventually, spontaneous arrest in size. Other parts of the body, such as nails or feet, are rarely affected Microsporids are uncommon. (For discussion of this aspect *see* Chapter 3.)

DIFFERENTIAL DIAGNOSIS

It is important not to miss the diagnosis of fungous infection and it is also important to classify the type of mycosis. It should be considered that patchy loss of hair from a child's scalp denotes ringworm until repeated laboratory investigation has failed to substantiate the diagnosis. When there is little inflammatory reaction, alopecia areata may be simulated In alopecia areata, however, there is a sudden complete loss of hair with no scaling on the surface of the patch Trichotillomania and trichokryptomania have proved puzzling to us in a few instances, but in such cases the child is usually neurotic, the apparent or actual loss of hair is near the front of the scalp, there is no scaling, and the patch is usually irregular.

Seborrheic dermatitis may be differentiated by the presence of greasy scales and the absence of patchy loss of hair The superficial form of favus may so closely resemble seborrheic dermatitis that only the lack of response to therapeutic agents favors a diagnosis of favus.

When marked inflammation is present, pyoderma is the chief condition to differentiate Pyodermic lesions on the scalp of a child usually spell pediculosis, and an inspection of the scalp ordinarily reveals nits. Pustular lesions, however, may appear secondarily to a focus of infection such as a discharging ear We have observed an instance of pustular lesions of the scalp due to the ingestion of iodine

Tinea amiantacea (asbestos-like tinea) was first described by Alibert in 1832 The disease has been reviewed by Becker and Muir It should probably be classed as a pseudomycosis, since no constant fungous flora is demonstrated It is important, since the clinical signs simulate those of

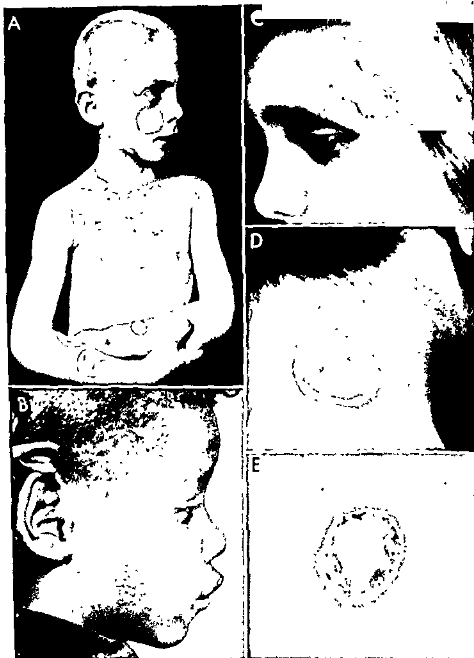


Fig 5 Microsporosis (M audouini) Glabrous skin lesions may be associated with disease in scalp, as in A In B and C, lesions are highly inflamed Prompt treatment prevented extension to scalp D, lesion with double rings E, acute circinate lesions on leg of young adult

tinea capitis It is thought by some to be a form of seborrheic eczema and by others to be an aberrant form of psoriasis. The disease is manifested on the scalp by a binding together of the proximal portions of the hairs by asbestos-like laminated scales It may be localized to one area or distributed over the entire scalp. Scaling is present on the involved surfaces but usually with little visible inflammation The disease is said to occur most frequently in children. There is no tendency to loss of hair, nor is the structure of the hair altered. The peculiar large yeastlike bodies which have been noted are probably artefacts caused by the action of potassium hydroxide on grease The condition is usually helped by frequent washing of the scalp and by the application of a salve containing sulfur or tar. Recurrence is common.

Trichorrhexis nodosa is a disease in which the hairs show one or more nodular enlargements Microscopically, these nodules are due to partial transverse fracture. When the fracture is complete, the end is frayed. A certain amount of thinning of the hair may result.

Monilethrix, a congenital disease, produces a variable degree of alopecia. The affected hairs have a peculiar undulating appearance due to regular variations in their diameter. Where the diameter is reduced, a fracture is apt to occur Keratosis pilaris is often associated, and generalized scaling of the scalp is common.

Recognition of the type of fungous infection from clinical features is not always possible, although one usually has a strong conviction In most instances of the M. audouini disease, there is little inflammatory reaction, whereas when M. canis is the cause the lesions are red and often tender. In M. gypseum (fulvum) infections, there is classically a solitary, boggy lesion In the Trichophyton infections, the involved hair may be broken off flush with the scalp, producing a black-dot appearance (T. violaceum), or there may be an associated greasy scale (T. schoenleini). In cases caused by T. tonsurans there is a considerable variation in the clinical features, and these will be reviewed when that type of trichophytosis is discussed.

In all cases of suspected infection, one is not justified in being content with a clinical diagnosis Examination of the scalp under filtered ultraviolet rays and microscopic examination of material such as hair and scales are mandatory It is highly desirable to inoculate a culture medium and determine the specific diagnosis Such procedures are simple to perform and yield exact information

PATHOGENESIS

Kligman should be credited with important basic conclusions from an experimental study in which he inoculated the scalps of both children and adults with two species of Microsporum His findings, correlated with those of others, may be reviewed under the headings clinical observations and mycopathologic interpretations

1. Clinical observations —Fluorescence was noted by the sixth to

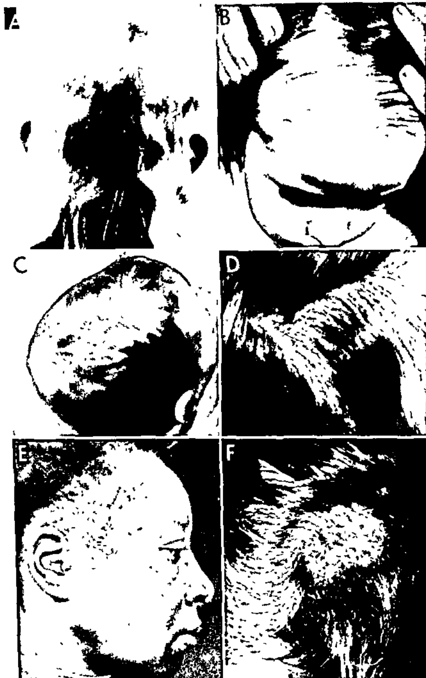


Fig 6. Diseases often confused with tinea capitis. A, trichotillomania B, alopecia areata C, psoriasis D, tinea amiantacea E, alopecia marginata F, trichorrhexis nodosa

seventh day in the lower portion of epilated hairs. After 12 to 14 days fluorescence could be detected without epilation. The circinate patch of tinea enlarged peripherally for from eight to 10 weeks and then stopped. Skin scrapings were then negative for filaments. About 5 per cent of hairs in a patch remain uninfected. Occasional hairs become involved without surface infection. The maximum size (climax) of the experimental lesions was attained in two to three months New lesions were rarely noted after three months. In seven children, reinoculation was attempted at a normal site after tinea capitis was present for at least three months. In five no new infection was possible, and in two only a localized take was obtained. As in the natural disease, not more than one-third of the scalp hair ever became involved before the refractory state developed (after approximately three months). The experimental infection was not treated, and spontaneous cure occurred in all instances, usually within seven months. The more extensive the manifestations the longer the duration of the disease, as in clinical experience with the naturally acquired infection. In adults, the manifestations were less pronounced and cure more rapid.

Kligman described four stages of the scalp disease. (1) an incubation period of a few days, (2) a period of spread lasting three to four months, (3) a refractory period, with no new lesions, and (4) involution with or without visible inflammation. He concluded that the use of X rays to treat only a limited part of the scalp might be sound if the disease was in the refractory stage.

2. Mycopathologic interpretations.—Biopsy sections removed from patients at intervals from the onset of infection with Microsporum to the natural end showed that by the third to fourth day the spores had germinated and a mass of segmented hyphae was present in the follicular orifice The arthrospores thus formed were of irregular shape. After the third day, filaments, often septate, could be found in surface scrapings. The enlargement of the patch of tinea capitis occurred by spread of the hyphae through the stratum corneum, the follicles being infected secondarily. No hyphae could be found in scrapings when the patch attained maximum size Individual lesions sometimes became involved without formation of a patch, in which case no hyphae were found in surface scrapings The filaments in the follicle were not present in the keratin lining the orifice but rather were entwined around the hair The hyphae always grew down and never outward A keratolytic enzyme present in the dermatophytes provides a method for obtaining nourishment. Kligman commented on the paradox that a luxuriant growth of hyphae "ignores" the presence in the follicle of sebum containing fatty acids known to be fungistatic

Reviewing the normal anatomy of the hair follicle, one recalls that the external root sheath of the follicle joins the epidermis above and the hair matrix below The follicle in children is 2 to 3 mm in length Keratin is formed by the external root sheath in the follicle for a small portion of the follicle above the level of entrance of the sebaceous duct The internal root

After development of Adamson's fringe, the external primary spores cease to be formed. However, ectothrix spores develop, in the mosaic pattern characteristic of Microsporum, being cuboidal or rectangular at first and rounder later. Just above Adamson's fringe, external hyphae appear, being lateral branches of the filaments in the cortex. These are short and twisted, resembling "densely interlocked deer antlers" Septations develop, and chains of cells (arthrospores) are formed. The cells separate from each other, and some are observed as a mosaic. The intrapilary hyphae are fewer as the hair progresses toward the surface.

In both ectothrix and endothrix infections the hair is invaded. In the former, spores may be observed either within or outside the shaft, whereas in the latter only intrapilary hyphae are formed.

In the rare instances in which a medulla is present, the fungus usually avoids it. Neither the medulla nor the internal root sheath is a satisfactory medium for fungous growth

Spontaneous cure is evidenced by a lessening in quantity of the intrapilary hyphae Fewer spores are produced, and the fluorescence decreases. Club, or resting, hairs are in a state of suspended activity. There are usually only a few intrapilary hyphae, these, however, may penetrate into the bulb, which in a club hair is completely keratinized. There are no ectothrix spores.

Inoculation of a plucked hair with a dermatophyte capable of causing tinea capitis never results in a typical invasion such as that noted in vivo. Kligman stated that "intrapilary growth is . . . impossible when the hair is not growing." Arrest of hair growth leads to arrest of fungous growth.

M canis (lanosum) infections are more rapid but otherwise similar to infection by M. audouini. Natural and experimental infections are identical histologically

Tinea capitis and tinea corporis are similar, since in both the skin surface is invaded first. The glabrous skin hairs have relatively short growing periods, the infection, therefore, cannot last for long.

Contrary to the usual clinical observation, there is an inflammatory response to the initial invasion of the stratum corneum Histologic findings include infiltration of lymphocytes in the upper cutis, often around blood vessels, spongiosis, and some acanthosis These reactions are probably incited by an exotoxin elaborated by the fungus It is of interest that the hair matrix and its papilla do not reveal any demonstrable reaction, even though the amount of fungous material is greater here than in the stratum corneum This is probably because of the thick, immature, hard keratin barrier between the hyphae and the matrix.

In tinea corporis the resultant inflammation creates an unfavorable medium for the invader Central clearing results The fungus continues to migrate peripherally Eventually it tends to burn out. T. rubrum and some other fungi are exceptions The cause of spontaneous cure, then, is interference with normal keratin formation.

sheath and the hair are formed by the matrix. The internal root sheath desquamates at the follicle mouth. The keratin, formed from the external root sheath, develops a tube, or cylinder, surrounding the hair.

During the period of invasion, the fungous elements are mostly confined within the tube and do not massively invade the keratin present so abundantly in the follicle. Bacteria follow the same pathway (O'Brien). The fungi continue to follow the hair deeper into the follicle and do not tend to invade the keratinized internal root sheath.

The hyphae outside the hair break up into short, rather large rectangular arthrospores Once the hair is invaded, the hyphae are long, with only infrequent septa. When the hyphae form outside the hair subsequent to invasion inside the hair, the arthrospores then formed are much smaller. During the early (follicular) phase, the fungus enters all follicles indiscriminately. However, club hairs, seen at times at the periphery of a patch of tinea, are resistant to invasion. In such hairs the fungi may be seen on the surface only.

On or after the sixth day after infection, the hair is penetrated Invasion takes place in a variable zone near the mid-point of the intrafollicular portion of the hair. Concomitantly, fluorescence is first noted. Kligman agrees with Davidson and Gregory that fluorescence is confined to that portion of the hair which is actually invaded.

Sabouraud described well the mechanics of hair invasion. The cuticle is penetrated and becomes stripped by the downward proliferation of the fungi. The cortex is then invaded. The filaments progress downward and between the ninth and 10th day reach their maximum depth. Because of branching, the mass of hyphae becomes increasingly more abundant near the base and at the bottom occupies most of the hair. Traction on the hair usually results in fracture and incomplete removal.

The hyphae in the cortex are long and have only infrequent septations After the 10th day the external hyphae tend to disappear Since the hair continues to grow toward the surface, the fungous material is gradually carried outward By the 12th day the point of penetration by the fungus has reached the surface and fluorescence may be detected. Adamson and Sabouraud knew that the filaments stopped short of penetration of the hair bulb The terminal hyphae are called "Adamson's fringe" This is within the hair, contrary to Adamson's original idea Kligman determined that penetration stops where the keratin originally developed by the matrix becomes mature. This is approximately 0 5 to 0 7 mm above the tip of the papilla A cross section reveals the fringe in an inverted V, since keratin develops laterally before centrally The hyphae do not penetrate into the nucleated zone Kligman pointed out that there is an equilibrium between the rate of growth of the fungus and the rate of formation of new hairs, so-called epidermal effluvial current (Wilson) If the hair grew faster than the fungus, the infection would be automatically extruded The fungus is unable to penetrate the nucleated keratin below Adamson s fringe

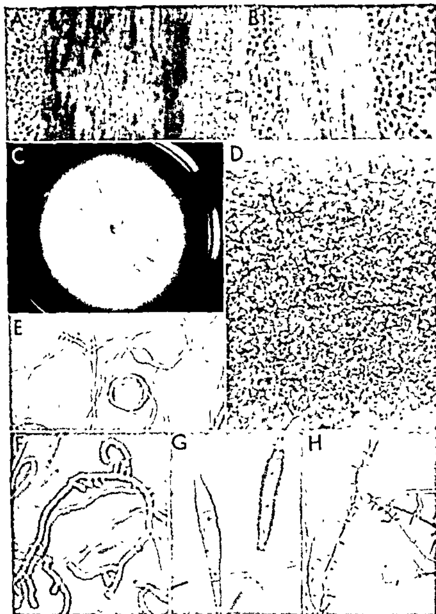


Fig 7. Microsporum audouini A, infected hair showing mantle of spores, × 370 B, longitudinal section of infected hair, invading elements within shaft and mosaic of spores surroundi[illegible] × 575 [illegible]
D, section of col[illegible]
E, F, G, and H, c[illegible]
bodies, × 460 G[illegible]
conidia, × 370

In tinea capitis there are multiple independent, hair infections. At first the follicles are equally susceptible. However, the hairs vary in susceptibility, some showing absolute resistance (i.e., club hairs). Occasionally, growing hairs also are resistant. Spontaneous cure results within two to five years, which is the length of the growing period of scalp hair. The hairs in the beginning of this life cycle, including new hairs following roentgen epilation, are not susceptible to infection by Microsporum, but this is not the case with Trichophyton endothrix fungi.

Infection of eyelashes and lanugo hairs terminates rapidly, as their life cycles are short. The resting stage may approximate the growing stage in length On the scalp, in contrast, over 95 per cent of the hairs are growing at any one time.

In kerion, damage to the matrix arrests the production of keratin. Lack of hair growth is responsible for spontaneous cure. This is contrary to the usual belief that cure is due to an allergic manifestation. Roentgen effect is also due to inhibition of keratin formation.

Spontaneous regression of infection is frequent and as yet unexplained.

Each infected hair is a separate colony, with the vegetative phase evidenced by the intrapilary hyphae and the ectothrix spores being the reproductive portion The infection is kept going by the proliferating hyphae of Adamson's fringe. Hyphae above this are relatively inactive. The ectothrix spores are not involved in the persistence of the infection. They are responsible for any further dissemination of the infection. According to Kligman, present day fungistatic agents do not reach the hyphae of Adamson's fringe and hence are incapable of any direct influence on the disease. Possibly they kill off some spores. Wilson stated the belief that the rate of growth of the terminal filaments advancing into the follicle can be slowed by the action of a fungicide on the mycelial parent mass nearer to the surface.

Growth of dermatophytes is limited to fully formed keratin. The sharp limitation of the infection in the hair to above the keratogenous zone suggests a biochemical inhibitor.

Only certain scalp areas are susceptible to infection, and other sites may not respond to experimental inoculation at any time

MYCOLOGY

1 Direct examination —The fungus appears in the form of a mosaic sheath around stubby hairs There is little tendency to chain formation. The individual elements, or spores, are round and small Boat-shaped structures, possibly fuseaux, have been described as occasionally seen in relation to hairs infected with M audouini and M. canis by Appel and Ansell, Felsher and Eirnberg, and Daniels Ajello called these spindle-shaped cells root sheath cuticle cells In infections of the glabrous skin, mycelium may be detected Lanugo hairs may occasionally be infected

2. Cultural characteristics —Beginning as a white feathery fluff,

any difficulty, as lack of fuseaux and a compact core rule out both M. canis and M gypseum.

IMMUNOLOGIC REACTIONS

Occasionally children with infection due to M. audouini have moderate reactions to the intracutaneous test dose of trichophytin. More frequently the reaction is slight or absent; in only a few instances have we observed strong reactions.

PROGNOSIS

Infections due to M. audouini are usually classed as resistant to treatment. It is well known that spontaneous cure occurs at or near puberty. It also has been well authenticated that many patients get well after the infection has been present for several months. After three to four months there is little or no spread The disease, in any case, will never last longer than two to five years, the latter being the outside limit that hairs remain in the growing stage. The presence of visible, spontaneous inflammation is always favorable and usually forecasts an early termination of the infection. Inflammation produced by the topical use of irritating chemicals does not usually have any effect on the hair matrix and consequently is not helpful.

TREATMENT OF THE SCALP DISEASE

1. Local therapy —Some form of local (topical) therapy is indicated in every case This is so even if one is among the large percentage of dermatologists who do not believe that there is any specific effect on the fungus situated deep in the hair shaft and, as Kligman has shown, in perfect equilibrium with the host. Others believe, like Wilson, that antifungal agents exert some influence on the growth of the fungus even indirectly and may be given credit for specific effect. It is agreed by all that topical fungistatic therapy should be used promptly in the hope that it will destroy some of the available spores and also form a protective mantle over the infected areas, so that the likelihood of new areas of infection on the patient's scalp will be lessened and spread of the disease to others may be prevented

In certain special situations and for the reasons mentioned, the use of local medicaments is the procedure of choice and may be the definitive therapy (*a*) When the patient is approaching puberty the tendency to spontaneous cure is greater than it is in younger children. (*b*) Because of unfortunate experience with roentgen rays, this modality may be in disrepute with a given patient, in a small community, and even in certain cities The error can usually be traced back to careless use of roentgen rays

the colony grows moderately into a grayish-white fluffy culture. Aerial growth is scanty. There is usually a central elevation Radial grooving may appear, especially on Petri dishes, but this is not constantly or even frequently found on dextrose agar. On maltose agar the formation of radial grooves is one of the chief characteristics. Secondary radial grooves may also form. *Pleomorphism is uncommon.*

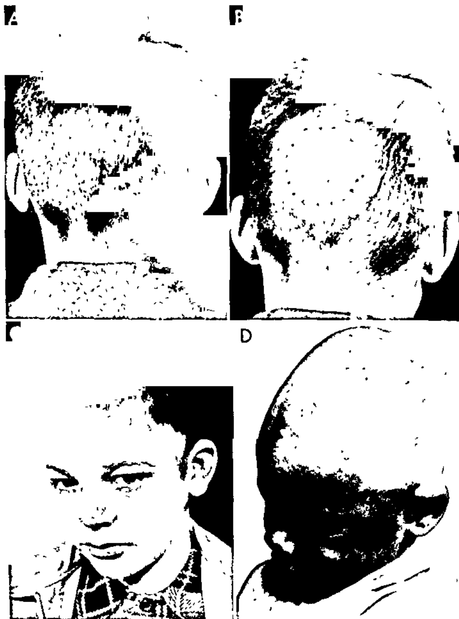
3. CULTURE MOUNT.—As a rule, fuseaux are found only occasionally. Hare and Taschdjian and Muskatblit reported strains which produced them in large numbers. Those observed by the latter authors resembled the fuseaux of M. gypseum. Microconidia are present in limited numbers Chlamydospores and pectinate bodies are frequent; they are more readily observed when cornmeal agar is used.

4 BIOPSY OF CULTURE.—The fringe consists mainly of short, coarse, filamentous fragments. Under high power magnification, occasional terminal chlamydospores are observed The core is deeply stained, with the coarse mycelium in close apposition losing its identity to form homogenous material in older specimens. Occasional racquet mycelium may be noted in the core The substrate contains sparse amounts of mycelium.

5 FILTERED ULTRAVIOLET RAYS.—The Wood light is extremely valuable not only in detecting infection but in determining its extent and also in following progress of the patient under treatment One is frequently surprised to find widespread involvement when clinical inspection had led one to believe that only one or two areas of infection were present. Furthermore, we have observed several patients in whom regrowth of hair in patches of partial alopecia due to a tinea infection was sufficiently vigorous to mask the disease Numerous infected hairs were observed by the test of fluorescence In the very early stage of infection the color may be noted only in the portion of the infected hair nearest the scalp. The short, stubby hairs found in patches of tinea capitis fluoresce as bright, clear green dots. Usually most of the hairs in a lesion are seen to be involved Beare and Walker reported the occasional occurrence of infected nonfluorescent hairs in infections of the scalp due both to M. audouini and to M canis Lanugo hairs in patches of tinea circinata may also fluoresce The cultural growth in 10 days is dull, clear and mouse-gray throughout

6 ANIMAL INOCULATION —Animals are resistant to infection with this fungus.

7 DIFFERENTIAL DIAGNOSIS (LABORATORY) —Direct examination of an infected hair will show Microsporum if it is present, since the spores are small, occur in large numbers, and have a mosaic arrangement outside the hair shaft On culture M audouini can be differentiated from M canis because M audouini begins to grow later, the young colony is white rather than yellow, and the appearance under filtered ultraviolet rays is dull and mouse-gray rather than bright blue and pink In the culture mount, fuseaux are rarely found, whereas in the culture of M canis fuseaux are normally present in large numbers Biopsy of the culture will assist if there is still



D

[illegible]

by someone ignorant of the necessity for exact technique in their administration. (*c*) If there is noticeable inflammation present, and particularly if there is in addition a positive reaction to trichophytin, expectant therapy depending on local applications will invariably be sufficient. (*d*) In the few instances of treatment failure following use of roentgen rays, the modality should not be repeated for six months. (*e*) On theoretic grounds, it may be inadvisable to administer X rays until the infection is three to four months old. In the meanwhile, vigorous local therapy may be instituted. It is customary to advise the parent to apply the medicament, usually in a grease base, morning and night, massaging it on to the entire scalp, taking at least 1 ounce of ointment each time, and spending at least three minutes in its application. The scalp should then be covered with a linen cap, which should be worn at all times A shampoo with plain soap to be given every other day may be advised. If the shampoo is carried out too vigorously or too frequently, the infected hair may be kept rubbed off close to the scalp instead of being epilated The result is that the infection does not respond as rapidly as expected The remedy is to lengthen the interval between shampoos and to use less vigor in applying the hand brush.

The following drugs and prescriptions are among the numerous remedies that have been advocated.

(*a*) Ammoniated mercury 3 to 5 per cent

(*b*) Thymol 1 per cent
Oil of cinnamon 0 5 per cent
Iodine crystals 0 5 per cent

(*c*) Sulfur 5 to 10 per cent

(*d*) Schwartz reported successful treatment of tinea capitis due to M audouini with the following formulas

(1)	Salicylanilide	5
	Hyamine 1622 (25 per cent)	5
	Carbowax 1500	100
(2)	S S copper undecylenate in carbowax 1500	
(3)	Pentachlorphenol	1
	Carbowax 1500	100

One of these remedies is applied daily for at least 40 days before improvement is to be expected Cure mav not be obtained with less than 100 applications A better effect is obtained in some instances by alternating the prescriptions

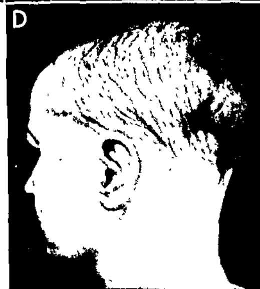
(*e*) Asterol dihydrochloride 5 per cent in solution or ointment base This should not be used in treating infants Symptoms of nervous system toxicity, including convulsions, are rare after the age of 2 years if not more than 2 ounces per week of the medicament is used

There is no evidence that the application of salicylic acid, chrysarobin, croton oil, oil of turpentine, and the like are specifically effective, and the use of such drugs is deprecated as unnecessarily hazardous

2. Epilation by hand —Since the infected hair is usually fractured if it is manually epilated, there is little to be gained by attempts to cure a patient by removing fluorescent stubs with forceps There is some belief that such labor is worth-while, since it favors penetration into the follicle by the prescribed medicament One should not place too much dependence


A

C

B

D

on this procedure. In cases in which only one or a few fluorescent hairs remain after the bulk of the infection is cured, destruction of the hair matrix and consequent cure may be undertaken by means of electrolysis, the needle attached to the negative pole of the galvanic current being inserted deep into the infected follicle.

3. ROENTGEN EPILATION.—Taking into consideration the situations discussed under "Local Therapy" in which topical application is indicated, X-ray therapy is still the treatment of choice in the majority of instances It is the most certain method for obtaining a prompt cure. However, it requires *expert technical knowledge derived from special training*; an X-ray machine that has been carefully calibrated, with the factors verified biologically, and constant care that the established routine is exactly followed

TABLE 6 —RETURN OF SCALP HAIR FOLLOWING ADMINISTRATION OF EPILATING DOSE OF ROENTGEN RAYS (figures based on average findings)

ELAPSED TIME, Mo	LENGTH OF HAIR, CM
2	soft down
3	1 0
4	1 3
5	1 9
6	2 7
7	3 8
8	4 4
9	6 7
10	7 0
11	8 6

If the dangers from gross overexposure are kept constantly in mind, one need have no fear that any untoward results will develop during routine use of X rays At New York Hospital, one machine is used for scalp epilation for both private and clinic cases. The reader is referred to Chapter XXVII in MacKee and Cipollaro's *X-rays and Radium in the Treatment of Diseases of the Skin* for details of technique. It may be emphasized that after the epilating dose of roentgen rays, the patient should be given an ointment containing 3 per cent ammoniated mercury When the hair begins to loosen (after 18 to 21 days), daily shampoos are in order On the 21st day after administration of the depilating dose of X rays, a cap consisting *of overlapping strips of adhesive plaster is applied and left on for 24 hours.* It is then removed, and most infected hairs which have not already been shed come with it *The patient should be carefully examined* under filtered ultraviolet rays for "sleepers"—broken-off stubs which evaded removal. Usually these can be extracted with forceps The patient should not be discharged before two examinations under filtered ultraviolet rays made one week apart, have indicated normal conditions A final inspection one month later is advisable

In patients with a limited infection we have occasionally used roentgen ray epilation only to the affected site (one or two exposures) Care should be exercised that small foci of infection are not overlooked, we usually

TREATMENT OF ASSOCIATED CUTANEOUS LESIONS

Although not common, associated areas of infection are seen occasionally, and the possibility of their occurrence in the patient, in other children in the family, and in a parent should be kept in mind. Such lesions respond well in most instances to the application of 5 per cent ammoniated mercury ointment or, if necessary, to an ointment containing 0.25 per cent anthralin (dihidroxy-anthranol). The latter should never be used near the face, because of the danger of conjunctivitis.

OTHER DETAILS

From what has been said it may be inferred that treatment of patients with microsporosis is simple and of routine nature. It is not always so, as the parents may not follow directions or agree to the treatment which is considered desirable. Most patients with this disease are found among the uneducated and unreliable portion of the population Consequently there is often difficulty in having the patients keep their appointments, and medicines prescribed for local applications are not always diligently applied In spite of these handicaps it is advantageous to spend some time with the parent and to explain carefully that:

1. Other children in the family should be examined for possible involvement even though there is no apparent infection.
2. The patient should not play with other children except under adult supervision.
3. The patient should not go to a barber or to the movies
4. Cure is not easy, because the infection is deep in the hair shaft. However, with co-operation by the patient, and with patience, a favorable result will be obtained.

PUBLIC HEALTH CONSIDERATIONS

Tinea capitis is not usually a reportable disease While sympathetic toward the problem, most health departments do not offer much help to physicians and clinics even when the incidence approaches epidemic proportions One of the questions is whether children showing the active disease should attend school. The matter may be argued at length, the main decision being as to whether [illegible] affected child attends school, [illegible] at home, idle and frequently under no supervision. In attending school the patient comes in contact with many more children and in practice is not usually kept from rough play In New York, the health department has removed restrictions which previously kept the patient from returning to school before being cured It is the impression of the department that

examine our patients several times, using filtered ultraviolet rays. If the duration of the infection is at least three to four months, there is little danger of further spread. The dose of roentgen rays administered should be one-tenth higher than that used with the five point technique. A salve containing 3 per cent ammoniated mercury is used after the treatment, and should be applied twice daily to the entire scalp. The scalp should not be washed After 21 days the grease may be removed by soap and water and by benzene and all loose hairs extracted by adhesive plaster. Negative findings from two Wood's light examinations one week apart should be recorded before the patient is discharged It should be emphasized that this method is suitable only for special cases of limited infection, particularly in girls for whom total epilation of the scalp is a minor tragedy. Despite all precautions, the result may be a failure, in which case three months at least, and preferably six months, should elapse before further X-ray treatments are given.

4. Other treatments.—The administration of thallium acetate is mentioned, since it has been employed to produce epilation. However, it is an extremely toxic drug and fatalities following its use have been recorded. Because of the danger of error in dose, and since even with amounts of the drug which are presumably safe there are still unwanted side effects, thallium salts should not be employed in treating tinea capitis.

For many years, the administration of estrogenic hormones either parenterally or by inunction has interested investigators. In a study by Lewis, Hopper, and Reiss of the effect on fungi of estrogenic and androgenic substances, an in vitro effect was obtained, but clinical results were poor when such agents were applied locally to areas of infection In a recent report, Dobes reported on the treatment of 280 male patients with estrone administered subcutaneously in doses of 10,000 units weekly to children below the age of 5 years and 20,000 units weekly to older children. The response was usually prompt and satisfactory It was manifested by loosening of the hair, which could then be manually removed, or gradual loss of fluorescence

We have attempted to cure resistant infections by means of vaccinotherapy (trichophytin), substitution of another fungus capable of producing an inflammatory response in the scalp, use of short wave ultraviolet radiation, and other modalities and methods, but without any consistent effects The poor results which we obtained from the therapeutic use of trichophytin were similar to those reported by other observers who studied their cases from the etiologic point of view. Cures attributed to trichophytin for the most part concern infections due to M canis, M gypseum, or T gypseum, and since these have a tendency to spontaneous cure, the role of trichophytin is debatable We have not been able to substantiate the claims made by a commercial concern for an imported trichophytin which has been extensively advertised as a certain cure for ringworm of the scalp

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this measure has not resulted in any demonstrable spread of the disease.

Careful examination of the scalp, including use of the Wood light, to screen children before admitting them to school, a camp, or an institution would appear to be a wise precaution.

Educational talks to lay people explaining the contagiousness of tinea and the advantage of avoiding contact with known cases of the disease are indicated. Barbers should be told that infected combs, brushes, and clippers will spread the infection. Washing the comb and brush with soap and water after each use and sterilizing the clippers would probably be sufficient to prevent infection. The physician should not send a patient with tinea capitis to the barber shop He might better remove the hair himself with hair clippers which he can sterilize. Barbers should be instructed not to cut the hair of a child with evidence of tinea capitis. Parents should be instructed to wash the child's scalp immediately after each haircut

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Fig. 10 Microsporosis (M. canis). A, multiple areas of partial alopecia with minimal inflammatory reaction B, acute inflammatory response (kerion), which is common C, extension of infection to glabrous skin of face D, follicular and glabrous lesions on back of neck

3. Microsporosis

(Microsporum canis)

IN MYCOSIS due to Microsporum canis, the scalp and glabrous skin of children are specially vulnerable and the lesions are usually inflammatory. Pets and laboratory animals are susceptible.

Synonymy: Microsporum lanosum; Microsporum felineum.

ETIOLOGY

The infection may be transferred from child to child or to an adult and is sometimes responsible for family outbreaks. In a housewife aged 42 with a scalp infection due to M. canis, English and Warin considered cicatricial alopecia to be a factor in lowering resistance. The infection is more often acquired from a pet, such as a kitten or pup. As in humans, the young of the species is most vulnerable and infection in the adult animal is rarely seen. M canis is ordinarily responsible for half the cases of microsporosis *seen in New York. Its incidence was only slightly increased during the* widespread epidemic of tinea capitis in the mid-forties. It is of interest that until recent years this fungus was the predominant finding in scalp ringworm in the southern and western parts of the United States. It is also curious that in the northern Pacific States, the infection is reputedly more resistant to therapy than its counterpart in some other geographic regions. In continental Europe, M canis is uncommon, but it is a frequent pathogen in England

CLINICAL CHARACTERISTICS

1 SCALP —The first manifestations may be redness and scaling of an area on the scalp Then broken-off hairs or total loss of hair is noted This initial patch enlarges noticeably within a few days, it is usually larger than any of the secondary lesions which are frequently scattered over the scalp At times the appearance is indistinguishable from that of lesions caused

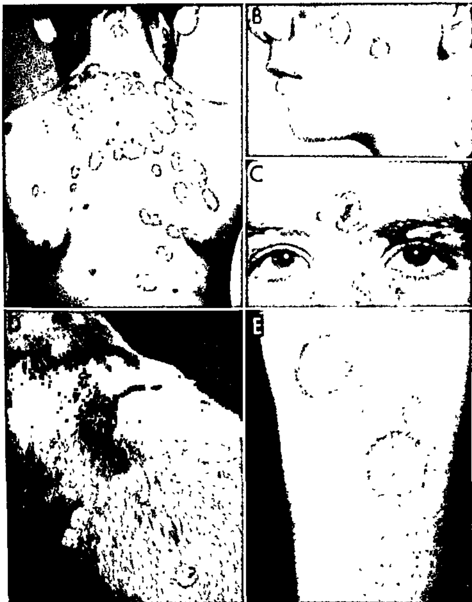


Fig 11 Microsporosis (M. canis). **A,** disseminated lesions with tendency to coalescence and double rings (an interesting immunologic phenomenon) **B,** circinate lesions in common location **C,** ringed lesions of impetigo contagiosa suggestive of tinea, typical crusted lesions, however, were present elsewhere **D,** tinea in dog belonging to patient in **B.** **E,** leg lesions acquired from kitten

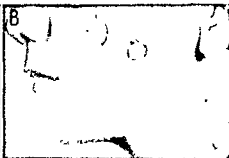
by M. audouini, but a noticeable inflammatory reaction, often complicated by pustulation of mild or severe degree, is more usual. A painful, infiltrated boggy mass (kerion) is present in one out of 30 cases Because of the tendency to spontaneous epilation, fewer broken-off hairs are noted than with M. audouini infection, and many M. canis infections proceed to cure within a few weeks. Since this disorder is susceptible to overtreatment, inflammatory flares and contact reactions to drugs are not uncommon.

2. GLABROUS SKIN.—Infections on the smooth skin are of common occurrence; they are more frequent in children but are occasionally found in adults, particularly the mothers of patients The lesions are usually circinate, with a clearing center and a vesicular border. Sometimes two or more concentric rings appear in a single lesion. If the infection is untreated, new lesions develop on skin adjacent to or remote from the original focus. Lesions are commonly seen on the face and neck of children with tinea capitis. The subjective symptoms are usually mild, although the infected skin is pruritic and subsequent scratching may contribute to spread. Infrequently, widespread infections of the glabrous skin occur. One of the most protracted instances of tinea glabrosa in our experience was that of a woman in whom over 100 circinate lesions developed; the therapeutic response to various types of treatment was poor.

3. NAILS AND BEARD —Lyons observed a 26-year-old woman with infection of the nails on both fourth fingers. The distal half of the nails was yellowish, opaque, and lusterless. Cultures yielded M canis. Cure was effected within eight weeks by local therapy. The origin of the infection was not ascertained Infection of the adult beard has been reported, but we have not observed a case.

4. DERMATOPHYTID (MICROSPORID) —Jadassohn, in 1911, before the Swiss Medical Congress, first described an eruption in patients with kerion consisting of small follicular elevations which occurred either in groups or diffusely and in large or small numbers and which disappeared spontaneously There was a resemblance to lichen scrofulosus, but the histologic picture was different and the patient's skin did not react to the injection of tuberculin There was a symmetric distribution, the trunk was the usual site, and often the extremities were involved as well. In some instances horny spikes, or spines, capped the lesions and the appearance was similar to that of lichen spinulosus The work of Jadassohn, Bloch, Guth, and others of their school soon showed that these rashes (and others resembling erythema toxicum and erythema multiforme) were expressions of cutaneous allergy due to a hematogenous spread from an inflammatory focus on the scalp We designate a rash of this character a dermatophytid. Fungi or their products cause sensitization of the skin, and this altered reaction results in lesions which in themselves are sterile We have observed a number of instances of dermatophytid in children with tinea capitis in which the rash followed a depilating dose of roentgen rays Sometimes strong topical applications causing marked inflammatory











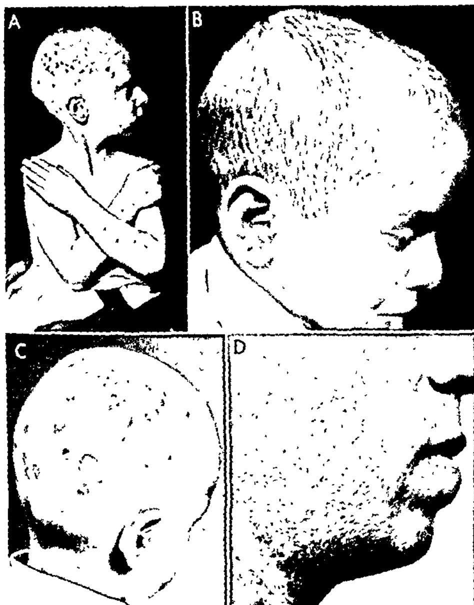
[illegible] A, disseminated lesions with tendency to coalescence [illegible]

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A
B
C
D

changes result in dermatophytid. In all instances of dermatophytid the patient exhibits a strong reaction to the intracutaneous test with trichophytin. The original focus is always an inflammatory lesion or lesions, most frequently frank kerion.

The subject is further discussed in Chapter 10

DIFFERENTIAL DIAGNOSIS

If the scalp reveals a spontaneous inflammatory reaction, this points to a zoophilic fungus or to pyoderma. In the latter disorder there is less tendency to hair loss and there may be an associated pediculosis. In instances of minimal inflammatory changes, clinical differentiation from infection due to M. audouini may be impossible.

PATHOGENESIS

According to Kligman, the mechanisms of invasion and host resistance are similar to those of M. audouini but take place faster.

MYCOLOGY

1. Direct examination.—The appearance in the sheath around the infected hair is indistinguishable from that of M. audouini infection in the same location. The individual spores are small and round and are present in clusters. Appel and Ansell have demonstrated structures resembling macroconidia in KOH preparations of infected hairs. Daniels made a similar observation, but his conclusions were somewhat indefinite. According to Ajello, such spindle-shaped cells are probably root sheath cuticle cells. On the smooth skin, mycelium is noted in sparse amounts Lanugo hair is sometimes affected.

2 Cultural characteristics.—Growth is moderately fast. A downy fluff appears, around which is yellowish pigment. In two weeks the central part of the colony is depressed The aerial growth is abundant and woolly. The color is a buff-tan. When grooves are present, they are often concentric but may be radial. Pleomorphism starts with regularity after four or five weeks. Considerable pigment of yellowish color is usually produced in the subsurface portion of the colony

3 Culture mount —The characteristic feature is the large number of fuseaux of the tapering variety (taken from the center of the growth). Their walls are thick and roughened There are from four to seven compartments Microconidia and occasionally racquet mycelium and pectinate bodies may be noted

4 Biopsy of culture —In two weeks there is a distinctive fringe consisting of deeply stained, variously sized reproductive bodies These are predominantly fuseaux of the tapering thick-walled variety Most are



serve to differentiate this disease from tinea circinata

sectioned, although an occasional whole fuseau may be noted. The core is well formed, with a close network of hyphae Mycelium of less staining intensity penetrates the substrate.

5. FILTERED ULTRAVIOLET RAYS.—*Whether on the scalp or extracted,* the infected hairs resemble those infected with M. audouini and are a bright, clear green. Within an affected patch, clear areas devoid of hair are often seen. Colonies of M. canis after 10 days are also bright and clear. The center of the growth may be lavender-blue, shell-pink, or flesh-ocher, the mid-*zone (not always present) is lavender-blue, the edge is olive-drab or mouse-*gray.

6 ANIMAL INOCULATION —Kittens and puppies as well as laboratory animals are readily infected. Because of this fact the organism is known as an "animal" or "zoophilic" Microsporum. The course of the primary infection as well as the results of reinfection have been studied by Reiss and collaborators. According to Georg, only 32 per cent of infected cat hairs fluoresce in filtered ultraviolet rays.

7. DIFFERENTIAL DIAGNOSIS (LABORATORY).—This is discussed in Chapter 2.

IMMUNOLOGIC REACTIONS

There is usually a moderate or vigorous reaction to the intracutaneous trichophytin test. In rare instances the reaction is not present

PROGNOSIS

Occasionally a patient having noninflammatory scalp lesions due to M canis responds poorly to local measures and requires roentgen epilation This situation is the exception The usual outlook is favorable for cure within a few weeks from topical treatment alone In most patients the response is fairly rapid, depending on the length of time required to achieve epilation of the infected hair A vigorous reaction to trichophytin is decidedly favorable The usual result for glabrous lesions is cure within a week or two *In rare instances there is a complete absence of resistance* to infection on the part of the patient This situation may occur in cases of infection with fungi that ordinarily cause acute inflammatory responses in the patient's skin Hazel and Lamb recorded the case of a girl, 23, who had gastrointestinal moniliasis and coincidentally a cutaneous rash due to M. canis The latter eruption was widespread on the face and body; the fingernails and toenails were involved The C albicans infection was of 14 years' duration, the manifestations of M canis had been present for seven years. Every possible form of therapy was administered without any consistent effect. We have observed several instances of resistance to treatment when cultural studies revealed a fungus which ordinarily responds satisfactorily within a short while Fortunately, instances of stationary infection, such as that of the patient of Hazel and Lamb, are rare.

TREATMENT

1. SCALP.—All patients with scalp manifestations of this mycosis should be given a trial of local treatment (*see* medicaments and directions in Chapter 2). It is our usual practice to begin with somewhat milder strengths than we use when M. audouini is responsible. We often prescribe an ointment containing 3 per cent of ammoniated mercury. In cases of severe inflammation, including kerion, it may be advisable to defer active drug therapy in favor of hot, wet boric acid compresses. For the success of such treatment it is necessary to apply the compresses for periods of one hour four times daily, keeping the treated site sopping wet during the time of application. In an occasional patient, particularly when there is very little inflammation, progress may be so slow that roentgen epilation is advisable. Microsporids are usually asymptomatic and are self-healing, requiring no specific treatment.

2. GLABROUS SKIN.—The time-honored application of iodine tincture is still useful. A strength of 1 per cent is best to avoid irritation. Other lotions which may be employed include commercial preparations containing fatty acids (Desenex, Timofax) or Asterol tincture. Ointments are often preferred. There is a wide selection, including ammoniated mercury 3 to 5 per cent; sulfur precipitate 3 to 5 per cent; a combination of salicylic acid 2 per cent and benzoic acid 4 per cent; fatty acids (Desenex, Timofax), and asterol Most schemes of treatment suggest applications of the medicament once or twice daily. It is rarely advisable to use more than one drug at a time, and the incompatibility of iodine and mercury and of mercury and sulfur should be kept in mind. It is better to use remedies in low concentration at first and observe carefully for any evidence of intolerance. Asterol should not be used on infants under the age of 2, and not over 2 ounces per week of the preparation should be applied to the skin of older children.

It is important to keep a careful watch on other children in the family or neighborhood, repeating the Wood light examination every week or two The Wood light may reveal fluorescence in infected pets and is therefore useful to trace the source, but, as mentioned, it is not always dependable.

As Georg has pointed out, the main source of infection would appear to be cats, and control of the disease in cats is important to prevent human infection She suggests that veterinarians accurately diagnose the disease, that cat-breeding establishments be inspected and regulated, and that stray cats be eliminated

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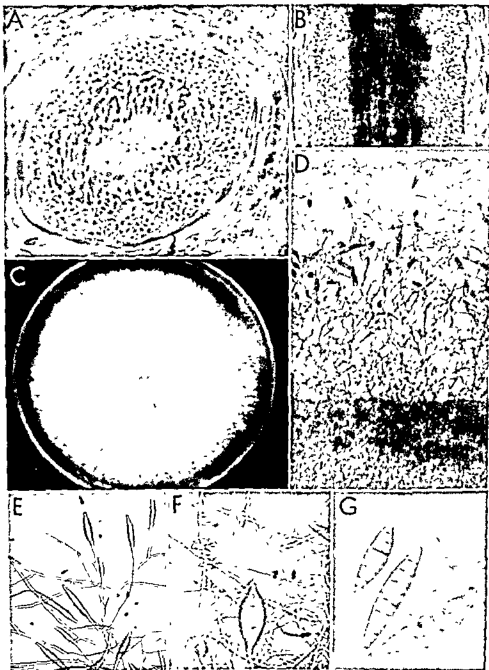


Fig 14 *Microsporum canis* **A**, section through cat's hair showing mantle of spores, × 600 **B**, mosaic of spores external to hair shaft × 300 **C**, giant colony after three weeks, of typical appearance **D**, section of colony showing macroconidia in filamentous fringe, core is composed of densely packed coarse filaments, × 100 **E**, culture mount showing pointed fuseaux, × 60 **F**, fuseaux with microconidia, × 300 **G**, thick-walled septate fuseaux, × 500

4. Microsporosis
(Microsporum gypseum)

MICROSPOROSIS due to Microsporum gypseum is a superficial, comparatively rare mycosis of the scalp and smooth skin, of world-wide distribution. The clinical features are an intense inflammatory reaction and a tendency to localization in one area.

Synonymy: Microsporum fulvum, Achorion gypseum.

ETIOLOGY

The majority of patients are children, although adults may also become infected. In New York, most instances of this infection have been observed in families who originated in South America. Ajello has reviewed the literature and has found that the disorder has been uncommonly observed on all continents and in most countries. The fungus has been isolated from horses, dogs, cats, and other animals. However, Ajello stated the belief that animal infection is less important than the saprophytic existence of the fungus in soil It is of uncommon interest that soil samples from the states of Tennessee, Georgia, Idaho, and Washington have yielded positive cultures of M gypseum The highest yield of positive cultures has been from samples which could have been contaminated by animals or on which hair or scales from animals could have been shed and thus provide suitable incubation medium Fuentes and his collaborators isolated M gypseum in seven out of 13 Cuban soil samples Small epidemics of the disease may occur, as reported by Whittle.

CLINICAL CHARACTERISTICS

Both scalp and glabrous skin lesions show a moderate to intense inflammatory reaction There is usually only one lesion and rarely more than three Occasionally there are a few satellite areas When the scalp is involved, the patch is erythematous, edematous, and often exudative and

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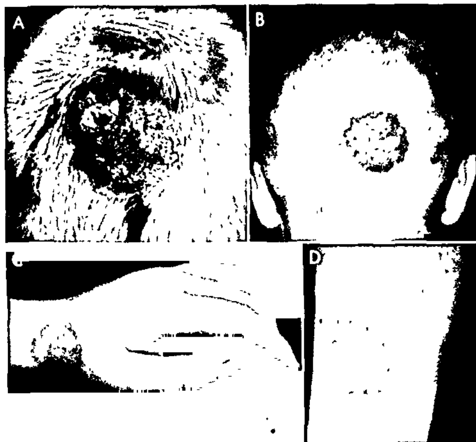


Fig 15. Microsporosis (M. gypseum). Usually there is a solitary lesion observed in a child **A**, highly inflamed, exudative, crusted, and boggy scalp lesion. **B**, well-demarcated, red, and edematous lesion **C**, solid plaque type with sharp margin and elevation above level of skin **D**, leg lesion which, under treatment, still shows evidence of pustulation.

crusted. The hair within the patch becomes loosened and ultimately is all shed. On the glabrous skin a ringed, erythematous lesion with a tendency to a clearing center and a vesicular border is the usual finding. The central portion may be scaly, or if the inflammation is intense, an exudative crusted surface may develop

DIFFERENTIAL DIAGNOSIS

This infection may be suspected when the patient presents solitary and highly inflamed lesions It usually has to be differentiated from an infection due to M. canis, although pyoderma may be simulated.

MYCOLOGY

1. Direct examination.—Hairs infected with M. gypseum may show a sheath of spores arranged in rosaries, probably representing the early stage of invasion, and also spores with no linear arrangement. The resemblance to an infection due to T. schoenleini is sometimes striking. When the invasive stage of the infection is over, the appearance of the fungi in fresh preparations is indistinguishable from that of other Microspora. The fungi in lesions of the smooth skin are noted as short chains of spores; usually the amount of fungous material is scanty.

2. Cultural characteristics.—Few fungi in culture are more easily recognized. The rate of growth is moderate, and in two weeks there is a central umbo, which may be white, surrounded by a flat, felty growth resembling suede The cinnamon-brown color of the entire colony is characteristic If any furrows are present, they are usually concentric rather than radial. The growth continues in an agar slant until the medium is entirely covered The margin of the colony is usually abrupt Pleomorphic changes readily occur and are evidenced by the appearance of white tufts on the surface of the colony.

3 Culture mount.—Numerous macroconidia (fuseaux) are present. The walls are comparatively thin and the ends are rounded A dwarf form, in which the macroconidia were short, was described by Fuentes and his collaborators Racquet mycelium and nodular organs may be found. Small round spores are to be seen in moderate numbers.

4 Biopsy of culture.—The fringe is deeply stained and contains numerous macrospores noted to be short, oat-shaped fuseaux There is no demonstrable core Hyphae penetrate the entire medium in a loose network

5 Filtered ultraviolet rays.—It is probable that certain strains fluoresce, while others do not Some infected hairs fluoresce as the light-green stubs characteristic of Microsporum infections This is contrary to the experience of some other observers The fluorescence of the hairs may not be noted in an edematous patch, in this case the diseased hairs may

have been spontaneously epilated or may be below the surface. The cultural growth is dull, clear, and cinnamon-brown throughout.

6. ANIMAL INOCULATION.—M. gypseum may be transferred to the young of several species of animals

7. DIFFERENTIAL DIAGNOSIS.—The microscopic picture may simulate that of the other Microspora, but if the infected hair has been recently invaded, short filaments in the hair shaft may suggest infection with T. schoenleini. The cultural growth is highly characteristic. The fuseaux are of slightly different character and more numerous than those of M. canis. Nodular organs are not seen in other Microspora. The findings on culture biopsy are confirmatory.

IMMUNOLOGIC REACTIONS

Intracutaneous trichophytin tests invariably elicit sizable reactions in patients with infections due to M. gypseum. This is not surprising in view of the character of the lesions.

PROGNOSIS

When the lesions are first observed there is usually a history of short duration (one month or less) The tendency is toward spontaneous cure. There may be residual atrophy or scarring with permanent loss of scalp hair, although usually there is complete recovery.

TREATMENT

One must exercise restraint in treating this mycosis. If irritating remedies are used there will be an accentuation of inflammation with increase in local tenderness Ointments of the order of 3 per cent ammoniated mercury may be applied morning and night. If a kerion is present, wet boric or saline packs should be advised

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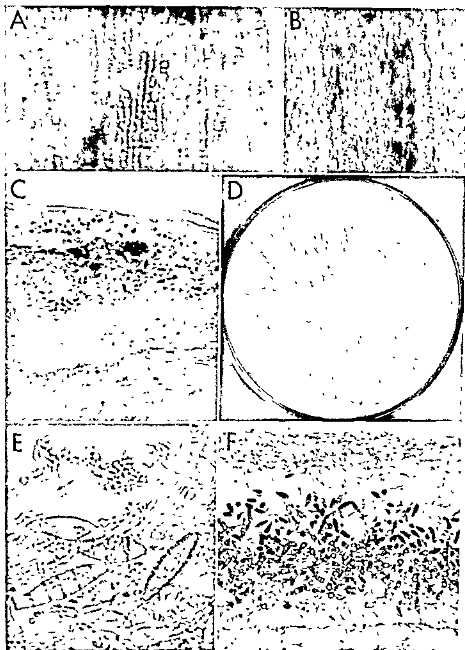


Fig 16 Microsporum gypseum. A, nonfluorescent hair, showing sparse segmented

5. Trichophytosis

(Trichophyton ferrugineum)

TRICHOPHYTON ferrugineum causes a superficial mycosis which chiefly affects the scalps of children and characteristically reveals little visible inflammation.

GEOGRAPHIC DISTRIBUTION

This disorder is endemic in Asia (China, Formosa, Japan), in some South Pacific Islands, in the Belgian Congo, and in Angola (Africa). It is rarely observed in the United States. We have isolated T. ferrugineum on three occasions: (1) from infected hairs which Lofgren, while on duty during World War II, sent us from American Samoa; (2) from the infected scalp of a Chinese child born in Hawaii, and (3) from a native-born child whose brother had recently returned from service in the Orient. No mention of T ferrugineum is made in Walker's Survey (1946–1949) of dermatophytes in Great Britain

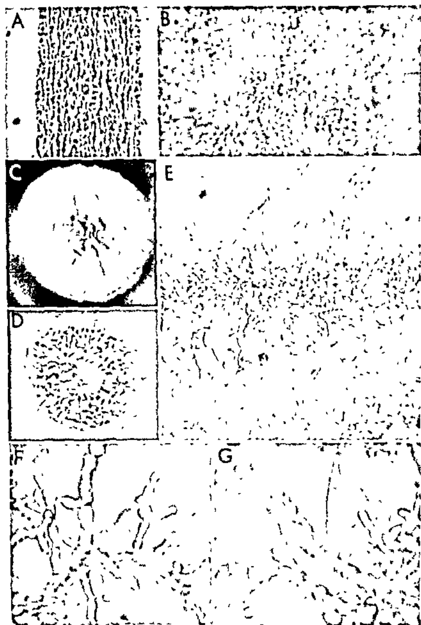
ETIOLOGY

According to the experience of Reiss in China, only native children are susceptible The disease is spread through contact with an infected child. Overcrowding and poor hygienic conditions contribute.

CLINICAL CHARACTERISTICS

There is a considerable resemblance to microsporosis (M. audouini). There is progressive, circinate, pseudoalopecia with breaking off of hairs and development of patchy lesions. Little or no redness is present, but some scaling develops With neglect the infection may involve extensive areas of the scalp Glabrous lesions are not infrequent, the face being most vulnerable The lesions are ill defined, scaly, and noninflammatory. There may be pseudoachromia in the affected site

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WILSON, J W., AND PLUNKETT, O. A.: Lack of fluorescence of scalp hairs infected with Microsporum gypseum (Fulvum), J Invest Dermat 16:119, 1951.



[illegible]

and poorly differentiated core, × 125 **F**, culture mounts with heavy elements resembling favic chandeliers, × 600 **G**, culture mount in which slender and coarse filaments intermingle, × 600

MYCOLOGY

1. DIRECT EXAMINATION.—The sheath of the invaded hair shows slender filaments (about 3 microns in diameter) packed tightly together and intertwined. At the level of the surface of the scalp, some spores may be found. Presence in scales has not been observed.

2. CULTURAL CHARACTERISTICS.—Growth is slow. Initially, after isolation, the colony is compact and golden yellow. Some strains have a reddish tone (Plate I, facing page 1). The center becomes elevated. Irregular

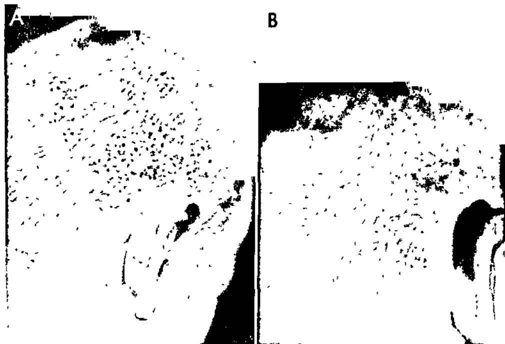


Fig. 17. Trichophytosis (T. ferrugineum). A, crusted and scaly patches with broken-off hairs B, 10 weeks later, with considerable improvement from topical treatment.

convolutions and radial grooves extend to the edge The edge of the colony is depressed in a narrow band beneath the surface of the agar The elevated central portion is glabrous, and the remainder of the colony except the narrow edge is downy white Vanbreuseghem described a white variety and four types of colony (1) waxy and cerebriform, (2) flat or with radiating folds, (3) scaly (the most frequent), and (4) downy

3. CULTURE MOUNT.—There is a paucity of spores Aleurospores are few and atypical Both terminal and intercalary chlamydospores are present. There are some racquet cells and occasional rudimentary pectinate bodies. The bulk of the mycelium is composed of closely intertwined, irregularly sized filaments with many protuberances

4 FILTERED ULTRAVIOLET RAYS.—According to Harukuni Urabe, Kyu-

6. Favus

(Trichophyton schoenleini)

A COMPARATIVELY rare mycosis in the United States, favus is still endemic and frequently observed in many parts of the world. The clinical manifestations are usually distinctive. The disease has historic interest, since it was one of the first disorders proved to be due to a fungus.

ETIOLOGY

The disease was formerly prevalent in Scotland and France but is less so now. It is said to be still common in Russia and in countries in southern Europe, North Africa, and Asia. In the United States, favus has been observed mainly in immigrants or their families. Several instances have been reported of small foci of infection. Small epidemics occasionally occur (Fishman, Inman) The disease usually develops in children but often persists into adult life Overcrowding, malnutrition, poor hygiene, and lack of recognition contribute to its spread An anomalous situation is seen when a solitary infected patient is discovered after many years of contact with others who have not become infected (Inman).

CLINICAL CHARACTERISTICS

The manifestations of this disease may be divided into (1) the active infection and (2) the late, residual phase

1 ACTIVE INFECTION —The scalp is the usual site Invasion of the surface of the scalp often results in a sulfur-colored, crusted, cup-shaped mass known as a scutulum The convex side presses down, while the concave side faces outward There is a tendency to adhere to the scalp, the mass being matted down by the hair Lack of personal cleanliness often contributes to its persistence If the scutulum is removed, a moist red surface becomes visible A typical "mousy" odor may be noted. Many hairs in

shu University, Katakasu Fukuoka, Japan, infected hairs always fluoresce as whitish-green stubs and consequently the Wood light examination is a most important diagnostic test so far as this fungus is concerned. The cultural growth in dextrose agar at one month shows a light yellowish-tan. The submerged periphery shows a bright cream color.

5. Animal inoculation.—No laboratory animal is susceptible.

6. Differential diagnosis —A fungous infection caused by T. ferrugineum should be suspected when the patient comes from the Orient. The infection may be widespread. The tendency to hair destruction down to the surface of the scalp may cause confusion with alopecia areata. The white-green fluorescence of the hairs, the cultural appearance, the fluorescent characteristics of the colony, and the lack of spindle spores in the culture mount suffice to differentiate the organism from Microspora.

PROGNOSIS

Untreated, the infection lasts for months or years.

TREATMENT

The only reliable treatment for the scalp disease is roentgen epilation. The glabrous lesions respond readily to 1 per cent tincture of iodine or to an ointment containing 2 per cent salicylic acid and 3 per cent benzoic acid.

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[illegible] 15 588, 1939

[illegible] Negroes

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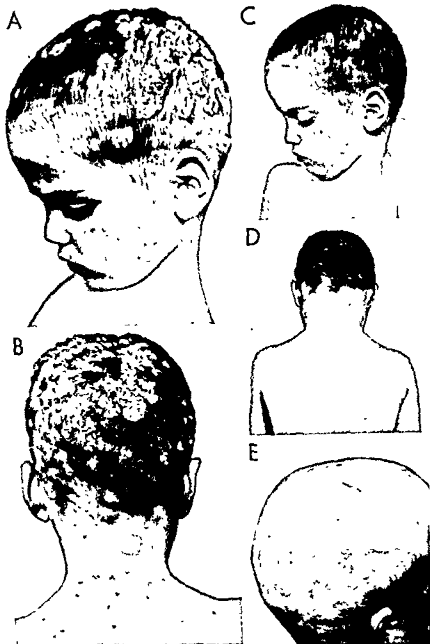


Fig 20 Favus in boy aged 6. Other members of family also were affected A and B, typical neglected crusted lesions (scutula) C and D, after daily use of soap and water and application of salicylic acid and sulfur ointment for one week, crusts have disappeared E, epilated scalp, showing residual erythema at sites of former lesions

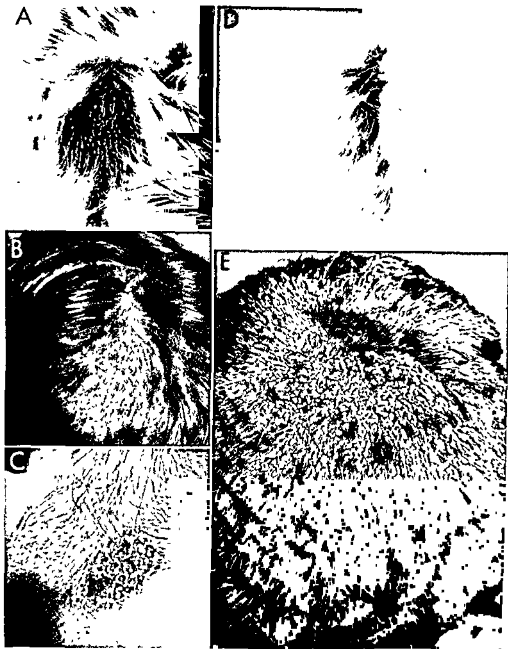


Fig 19 Favus (T schoenleini) Active disease affecting scalp **A**, early single patch with crusts but no alopecia **B**, untreated patient, with disease of short duration, showing thick crusts but no demonstrable atrophy **C**, group of scutula along hair margin **D**, adherent crusts with small atrophic areas, process was of 15 years' duration **E**, extensive involvement of scalp, disease had been unrecognized and untreated

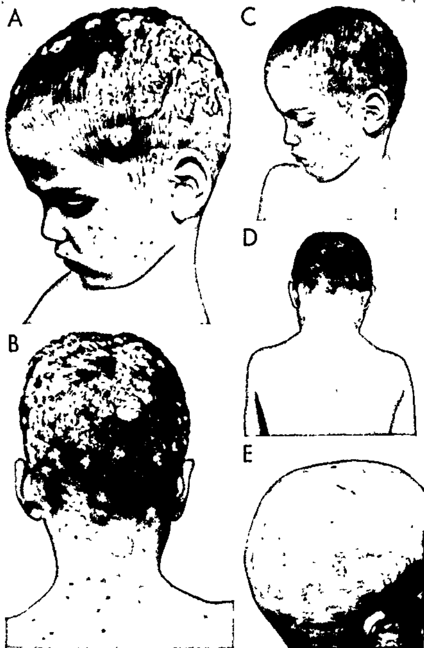


Fig 20 Favus in boy aged 6 Other members of family also were affected A and B, typical neglected crusted lesions (scutula) C and D, after daily use of soap and water and application of salicylic acid and sulfur ointment for one week, crusts have disappeared E, epilated scalp, showing residual erythema at sites of former lesions

the area become decolorized and may fracture, although other involved hairs retain their entire length. After weeks, months, and years, spreading occurs to multiple areas over the scalp. In addition, and particularly if the disease is untreated, similar scutula form on the glabrous skin. Rarely a nail may become involved, the condition resembling onychomycosis caused by *T. rubrum*.

Atypical manifestations are not unusual. When the infection is acquired in adult life and in persons with good habits for cleanliness, typical scutula may not develop. Thick diffuse crusting or seborrhea-like scaling, with a less pungent odor but resistant to treatment, may pose a diagnostic problem unless favus is kept in mind. In atypical forms, there is less alopecia than with scutula. Vesicular lesions (favus herpeticus) or scaly dull-red plaques on the smooth skin have been described.

2. Late residual phase.—In time, even without treatment, the infection burns out. However, the patient is stigmatized throughout the remainder of life by recognizable residua—permanent alopecia accompanied by atrophy and sometimes scarring. The alopecia is in patches of irregular size and outline which often coalesce to cover an embarrassingly large area over the front and top of the scalp. It is common to find evidence of the active disease on the scalp coincidentally with the sequelae noted.

DIFFERENTIAL DIAGNOSIS

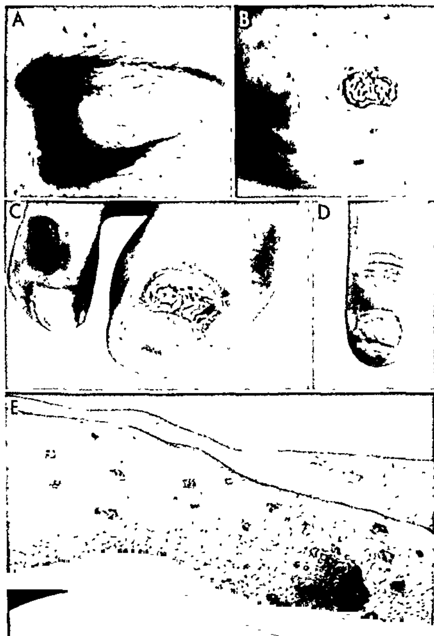
In a typical case there will be no difficulty in diagnosis during the active phase if favus is kept in mind, as the features are distinctive. When scutula are absent, seborrheic dermatitis may be closely simulated, in which case the fluorescence test and laboratory demonstration of *T. schoenleini* will be required. The late manifestations may simulate alopecia cicatrisata or discoid lupus erythematosus. In one instance we had difficulty in deciding whether the patient, an adult, had residua from favus or from roentgen irradiation administered as a child for the treatment of microsporosis.

PATHOLOGY

A cross section of a scutulum reveals a tangled mass of hyphae. Some hyperkeratosis is present at the periphery.

MYCOLOGY

1. Direct examination.—Large spores in chains may be found within the hair substance. Air spaces may also be noted in the hair, and air bubbles may be attached to it; this finding should always direct suspicion toward *T. schoenleini*. If a scutulum is examined, a mass of sporulated hyphae will be found. Material from the superficial lesions of the


A
B
C
D
E

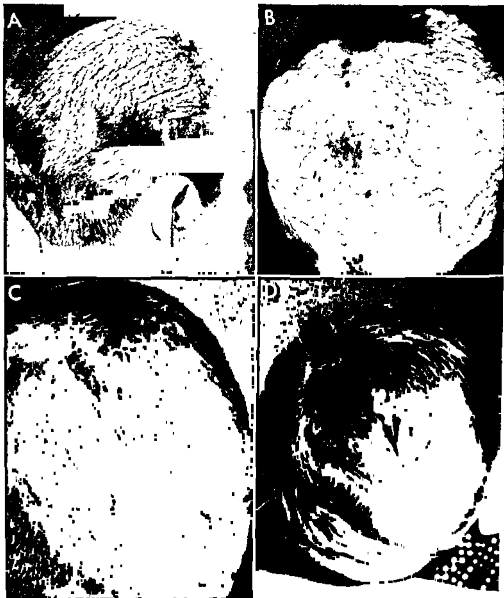


Fig 22 Favus (T schoenleini). Atrophy with permanent alopecia is invariable result in cases of long duration **A**, young adult from Afghanistan with loss of hair over crown **B**, result of neglected infection with extensive atrophy **C**, central atrophy and active crusting along border **D**, same patient with active disease controlled by manual epilation of infected hair

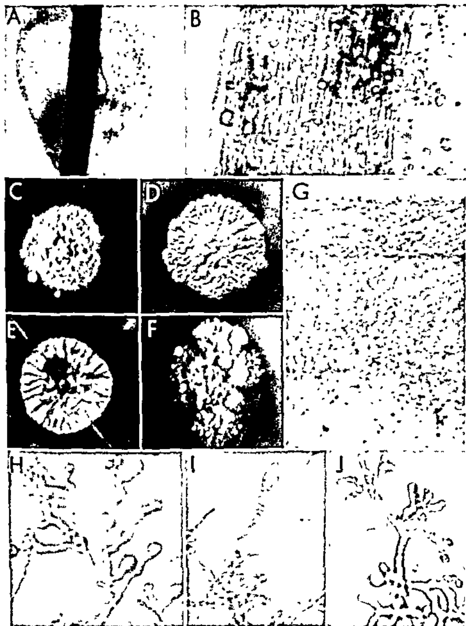


Fig 23. Trichophyton schoenleini A, hair surrounded by scutulum composed of filaments and spores × 30 B, irregular filaments and spores in hair shaft accompanied by air bubbles, × 270 C, D, and E, recently isolated organisms after six weeks' growth on dextrose agar F, typical growth after repeated transplants, note splitting of agar G, section through colony showing lighter hyphae in upper fringe, lower fringe and core reveal coarse filaments tightly packed H, culture mount showing irregular heavy elements I, culture mount with abortive type of fuseaux J, favic chandeliers (H, I, and J, × 500)

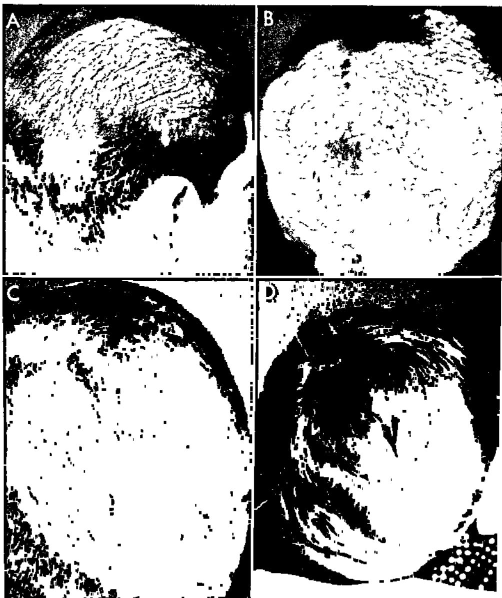


Fig 22 Favus (T. schoenleini) Atrophy with permanent alopecia is invariable result in cases of long duration **A**, young adult from Afghanistan with loss of hair over crown **B**, result of neglected infection with extensive atrophy **C**, central atrophy and active crusting along border **D**, same patient with active disease controlled by manual epilation of infected hair

TREATMENT

As with other types of resistant tinea capitis, the prompt administration of roentgen rays offers the best hope for early eradication of the infection. Preliminary therapy for one to two weeks to remove the crusts should include a daily shampoo with tincture of green soap and the rubbing on twice daily of an ointment containing drugs such as salicylic acid 3 per cent and sulfur 6 per cent. The same grease may be applied during the three weeks after the depilating dose of X rays has been given.

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smooth skin reveals a sparse number of hyphae. The findings in material from infected nails resemble those of other organisms, i e., chains of spores.

2. CULTURAL CHARACTERISTICS.—The rate of growth is slow; sometimes three weeks elapse before the primary colony has developed sufficiently to be recognized. The growth is compact and smooth and presents a characteristic waxy appearance. The surface is markedly uneven. Pleomorphism is uncommon. The colony grows down into the medium and in time produces cracking of the agar.

3. CULTURE MOUNT —Favic chandeliers are noted, they are diagnostic. Chlamydospores in large numbers may also be observed.

4. BIOPSY OF CULTURE.—The gross specimen is tortuous. The fringe is irregular, narrow, and closely attached to the core and consists of lightly stained hyphae. No microspores are observed. The core consists of both medium-sized and giant hyphae. When sectioned, the latter might be mistaken for chlamydospores or air bubbles. Less than half of the substrate is invaded with a sparse amount of mycelium. Occasional chandeliers may be seen

5. FILTERED ULTRAVIOLET RAYS.—Infected hairs show a greenish fluorescence but are less luminous than hairs infected with Microsporum. The cultural growths have a dull clear olive-gray appearance throughout.

6. ANIMAL INOCULATION —Guinea-pigs may be infected. The organism is also inoculable into rats, mice, cats, and rabbits (Dodge).

7. DIFFERENTIAL DIAGNOSIS.—The infected hairs are not always short. The appearance of a direct mount reveals an *endothrix infection*. The number of filaments is less than with other organisms; the presence of air bubbles is also highly suggestive, and the irregular segmentation of the filaments is characteristic. On culture, little difficulty is experienced in differentiating other growths The favic chandeliers visible in a culture mount are seen in no other cultural growths The culture biopsy reveals no microspores in the fringe and an admixture of giant filaments and medium-sized hyphae in the core.

IMMUNOLOGY

The majority of patients with favus show negative reactions to the intracutaneous test with trichophytin Occasionally a mild response may be noted.

PROGNOSIS

If appropriate treatment is instituted early, the disease may be cured without sequelae When the disease in its typical form has been present for several months, treatment may cure the activity, but the late effects will remain.

TREATMENT

As with other types of resistant tinea capitis, the prompt administration of roentgen rays offers the best hope for early eradication of the infection. Preliminary therapy for one to two weeks to remove the crusts should include a daily shampoo with tincture of green soap and the rubbing on twice daily of an ointment containing drugs such as salicylic acid 3 per cent and sulfur 6 per cent. The same grease may be applied during the three weeks after the depilating dose of X rays has been given.

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7. Trichophytosis

(Trichophyton violaceum)

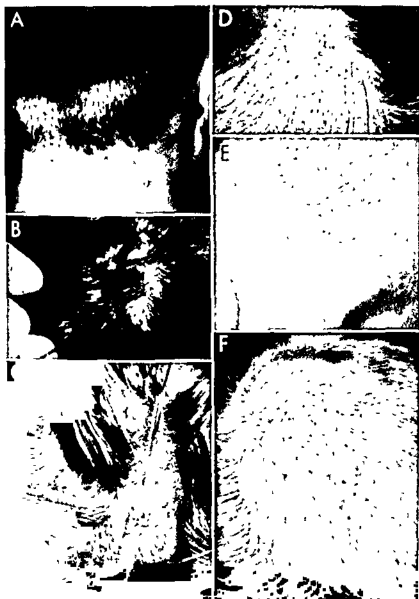
TRICHOPHYTON violaceum causes a superficial mycosis *usually manifested by so-called black-dot tinea capitis.*

ETIOLOGY

T. violaceum is widely distributed throughout the world, being a common cause of infections of the scalp, beard, and nails in Russia, Poland, and Italy as well as in other European countries and states in the Near East. In 1955, a report from Israel on tinea capitis revealed that of 1,038 positive cultures, 80 per cent were T. violaceum. The microorganism is not unknown in Australia. In the United States, it is found chiefly in immigrants or their siblings, but sporadic cases have been noted in native stock. Most of the initial infections occur in children, but the disease may persist into adult life.

CLINICAL CHARACTERISTICS

Infections caused by this fungus are usually insidious in their development and exceedingly refractory to treatment. On the scalp, the hairs are attacked and break off close to the skin. There is usually a minimal inflammatory reaction localized to the perifollicular tissues. Small pustules and follicular crusts tend to form. Permanent scarring may result. Kerion develops in 1 per cent of patients (Dostrovsky *et al.*). Mildly inflammatory lesions similar to those on the scalp may appear on the male beard. When the infection spreads to the nails, rarely more than one or two become affected. The nails are crumbly, yellowish, and opaque. In this location the fungus may be difficult to demonstrate. Lesions of the glabrous skin occur in less than 1 per cent (Dostrovsky *et al.*). The duration of the infection is usually many months or years.



spersed with active disease F, hair cut in patch around infected site, occasional crusts mark site of pyogenic superinfection Atrophic areas mark sites of permanent alopecia

MYCOLOGY

1. Direct examination.—This organism is an endothrix Trichophyton, invading the hair shaft. The spores are larger than those of Microspora and are arranged in rows or beads. No fungi are found on the surfaces of the hairs. In scales or nail tissue, the organism is also observed in the form of sporulated mycelium.

2. Cultural characteristics.—The rate of growth is slow, at prime the colony is small and well defined. It is smooth, shiny, compact and almost yeastlike, with a typical deep violet color. The surface shows convolutions, and usually radial grooves appear near the periphery. In old cultures the color may fade. Pleomorphism is rare.

3. Culture mount.—No free conidia or thyrsi are found. The mycelium is short, with numerous septa. Many irregular and bizarre branches are present. *In older cultures, chlamydospores are numerous.*

4. Biopsy of culture.—The fringe is the most prominent part of the section. It is darkly stained and well demarcated; in a six-week growth it consists of loosely arranged, coarse hyphae, microspores, and, deeply, many chlamydospores. The core is more lightly stained and the hyphae are in a lacy network with some homogenization. A few mycelial strands may be seen in the substrate near the core, but the remainder of the substrate is almost free of hyphae. In an achromatic growth of T. violaceum, the fringe was well demarcated and consisted of deeply stained threads. The core was not so intensely stained, and there was very little in the substrate

5. Filtered ultraviolet rays.—An infected hair differs in appearance from a hair infected by one of the Microspora. The dull whitish fluorescence is sometimes difficult to see well because the hairs are embedded in scales As in most compact growths, the colony is dull but clear. The *color is unchanged from that appearing in normal light. In practice, one* seldom relies on the fluorescence test to make a diagnosis, since the clinical features seldom simulate microsporosis.

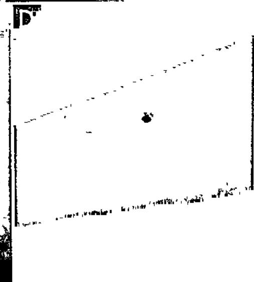
6. Animal inoculation —Successful transfers of this fungus have been made to many animals, including guinea pigs, dogs, and cats This is surprising when one considers the lack of inflammation in the human disease

7 Differential diagnosis (laboratory) —On a direct mount of an infected hair, the microorganism is seen invading the hair shaft It is to be further differentiated from other endothrices, such as T. schoenleini and T. tonsurans T violaceum is the most likely endothrix if the infected hair is short and twisted The differential diagnosis is based on the characteristics of the colony and on the appearance of the culture mount Favic chandeliers are seen only with T. schoenleini T. tonsurans shows large numbers of microconidia. The culture biopsy reveals the coarsely filamentous fringe to be more deeply stained than the core.


A


B





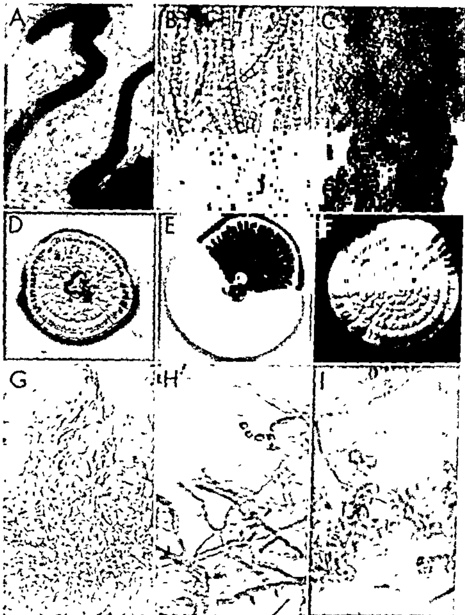


Fig 26 Trichophyton violaceum. **A**, serpentine appearance of infected hairs present in follicular crust, × 30 **B**, early invasion of hair, showing involvement of shaft with large spores arranged … iter, hair packed with spores, × 300 **D**, viola- … **E**, glabrous, dark colony with white sector- … fer from white sector, with colony showing … e colonies were four weeks old) **G**, section … avy filaments loosely packed and finer tufts … × 120 **H**, culture mount with both types of hyphae, × 500 **I**, rarely demonstrated microconidia in culture mount, × 600

IMMUNOLOGY

Negative or very slight reactions are noted after the intracutaneous trichophytin test.

PROGNOSIS

This is a difficult disease to cure. Relapse is common after an apparently good result.

TREATMENT

In the scalp disease, roentgen epilation is indicated. The patient should be followed carefully for at least two months after the initial defluvium, manual epilation being used to remove all the remaining stubs. In the series of cases reported from Israel, X-ray epilation was used in the treatment of 5,904 patients, with a recurrence rate of only 2.5 per cent This excellent result was attributed to meticulous aftercare, which included prolonged observation and painting of the scalp with tincture of iodine beginning after the initial defluvium

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8. Trichophytosis

(Trichophyton verrucosum)

TRICHOPHYTON verrucosum causes an inflammatory mycosis seen chiefly in rural communities and often producing family infections The glabrous skin and the hair follicle are vulnerable.

Synonymy. Trichophyton album, Trichophyton discoides; *Trichophyton ochraceum; Trichophyton faviforme.*

ETIOLOGY

The origin is often an infected animal (cattle) Several members of a family may be affected Children are specially vulnerable The disease has been reported from Iowa, Manitoba, Pennsylvania, upper New York State, and Staten Island, N.Y., and probably exists in other sections of the country. It is a common cause of ringworm in cattle in England (Ainsworth and Austwick). Wilson traced several instances of infection in laboratory workers to rabbits and white mice

CLINICAL CHARACTERISTICS

The initial lesion on the glabrous skin is a papulovesicle which soon becomes purulent The disorder spreads rapidly, and there is considerable redness and edema. The result is development of configurate or circinate plaques with elevated, often pustular, borders Edematous pustular lesions (agminate folliculitis) may also develop Kerion is common when the scalp is affected The male beard is sometimes involved with boggy infiltrations

DIFFERENTIAL DIAGNOSIS

The rapid spread, acute inflammation, and tendency toward configurate areas are suggestive One's suspicion is aroused if the patient lives in a rural community.



Fig 27 Trichophytosis (T. verrucosum). A and B, acute, rapidly spreading infection in sisters, aged 13 and 17 Ringed and configurate edematous and crusted plaques are distinctive Identical location in the two girls was due to their both wearing an infected dress C, boggy tumefaction in dairy worker

HISTOPATHOLOGY

Birt and Wilt studied the histologic picture in 10 cases and reported as follows:

Spores were seen within the hair shaft and in the lumen of the hair follicle Hyphae were present in the inner cornified layer of the follicle Despite an intensive search throughout the section, no fungi were found elsewhere. The hair in the involved follicle showed varying degrees of degeneration Where complete degeneration had occurred, the follicle in many cases contained numerous polymorphonuclear leucocytes.

The histologic picture varied considerably in different cases The epidermis was involved in all In early lesions inflammatory cells were confined to the superficial dermis and surrounded the hair follicles The cells consisted of lymphocytes and polymorphonuclears in about equal numbers. Some intraepidermal edema was evident, together with prolongation of the rete pegs.

In well-established lesions the reaction was complex, involving the epidermis and the dermis to the deepest part of the section (3 to 4 mm). The inflammatory cells were predominantly plasma cells with a few scattered lymphocytes, large mononuclears, and polymorphonuclear leucocytes. Collections of polymorphonuclear leucocytes (microabscesses) were seen throughout the dermis In some cases numerous eosinophiles were present in the deeper parts of the tissue Collections of three to four giant cells of foreign body type, with a few epithelioid cells, were found throughout the dermis in some instances

The epidermis in these advanced cases was edematous, with prolongation of the rete pegs, in one case epidermal changes were sufficiently marked to simulate pseudoepitheliomatous hyperplasia A number of microabscesses were seen within the rete pegs

It would seem that the initial phase is the extension of the fungi down the hair shaft with invasion of the inner layers of the follicle. The first reaction to this is simple and confined mainly to the superficial dermis and around the appendages The next stage is the extension of this process throughout the dermis, the infiltrate being made up predominantly of plasma cells. Finally the entire dermis is involved in a granulomatous type of reaction with localized microabscesses The abscesses must tend to coalesce to give rise to the large collections of pus that are so evident clinically

MYCOLOGY

T verrucosum is classified as an ectothrix Trichophyton.

1. Microscopic features —Masses of large spores in filaments may be observed

2 Cultural characteristics —The primary isolation is sometimes best accomplished at 37 C If there is considerable secondary infection, Littman s medium or modified dextrose agar may be inoculated The growth is slow, it may be stimulated by the addition of thiamine and inositol (Georg) Small yellow glabrous or waxy colonies, mostly subsurface, gradually form areas of velvety surface with a pattern of irregular radial folds and elevations

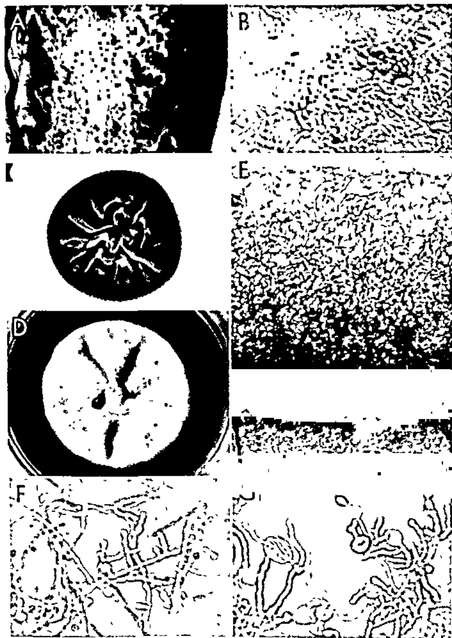


Fig 28 Trichophyton verrucosum A, section of infected hair with chains of spores

3. CULTURE MOUNT.—Vegetative elements are simple, delicate, and undifferentiated Chlamydospores are numerous No free spores, fuseaux, or chandeliers are present.

4. BIOPSY OF CULTURE.—The fringe consists of a loose network of mycelium with some microspores. The core is exceedingly dense, deeply stained, and relatively amorphous. A mycelial network extends deeply into the substrate, with gradual reduction in the amount of material.

5. FILTERED ULTRAVIOLET RAYS.—Infected hairs do not fluoresce. A soft, pinkish-lilac color develops in the colony.

6 ANIMAL INOCULATION.—Infection is difficult to reproduce in laboratory animals.

7. DIFFERENTIAL DIAGNOSIS (LABORATORY).—The colonies of this organism and of T schoenleini may be similar. The velvety surface and regular pattern of grooves are usually distinct The absence of chandeliers is helpful.

In the culture biopsy, the presence of microspores in the fringe and one size of hyphae in the core are against T. schoenleini

IMMUNE REACTIONS

The trichophytin test elicits strong reactions.

PROGNOSIS

In the majority of instances the disease is self-limited Treatment ensures a prompt response.

TREATMENT

Hot wet dressings of boric acid solution and local measures of nonstimulating mild type are indicated Manual epilation is helpful Good personal hygiene is desirable to prevent spread to others in the family

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9. Trichophytosis

(Trichophyton tonsurans)

AN INCREASINGLY important mycosis of world-wide distribution, trichophytosis (Trichophyton tonsurans) offers a challenge both in diagnosis and in management.

Synonymy. Trichophyton acuminatum; Trichophyton cerebriforme, Trichophyton crateriforme, Trichophyton sulfureum.

ETIOLOGY

The majority of patients are children, but the disease is not uncommon in adults Pipkin of San Antonio found T tonsurans to be the responsible fungus in 42 of 57 adult and adolescent patients with tinea capitis It is of interest that 39 were females and only three were males. In contradistinction to the predominance of male children affected by microsporosis (M. audouini), there is little difference in the sex incidence in children infected with T tonsurans.

The geographic distribution of the disease is of interest T. tonsurans is a common isolate in Mexico, accounting for 92 per cent of all cases of tinea capitis in a series reported by Ochoa and Vasquez In Puerto Rico, Carrion and Silva found the percentage of T. tonsurans infections to be 42 8 of all instances of tinea capitis The organism is also an important isolate in most countries in Europe and Asia In a survey conducted by Pipkin, this mycosis was found to be widely distributed over the southern half of the United States from coast to coast He noted endemic foci in Texas, Oklahoma, California, Utah, and Georgia, the infection reaching almost epidemic proportions in some parts of Texas and southern California Howell, Wilson, and Caro also found this mycosis not uncommon in Texas and California Cases have been reported from Arizona Indiana, Maryland, Michigan, and Ohio The disease is occasionally seen in New York, Chicago, and other large cities, and more frequent recognition probably accounts for its apparent increase in these places As with most other



boggy [illegible]
eventually a complete regrowth of hair in areas [illegible]

superficial fungous diseases, overcrowding and poor hygienic conditions are important predisposing factors. Pipkin was able to trace the source of the infection to a beauty parlor where the operator had the disease in her nails, to a maid whose nail disease was transferred to her mistress' scalp, and from a customer to a beauty parlor operator who infected her own scalp and later the scalp of an 11-year-old child.

CLINICAL CHARACTERISTICS

The scalp, nails, and glabrous skin may be affected.

The scalp disease is manifested by a wide variety of clinical pictures. It has been thoroughly studied by Pipkin and also by Howell, Wilson, and Caro. At one extreme there is minimal involvement and at the other severe inflammation. The disease may simulate other scalp disorders At times atrophy and scarring are sequelae. The following types of scalp involvement have been observed.

1 Hair invasion without visible scalp inflammation. The disease may be discovered by accident, being evidenced solely by broken-off hairs. These may be present as stubs or as black dots, usually scattered over the scalp and not in patches.

2. A mild inflammatory, seborrheic-like generalized scaling associated with thinning, which is often linear. The scales may be dry and the stubs inconspicuously hidden beneath them.

3. Disseminated patchy loss of hair with scaling, stubs, and black dots.

4 Perifollicular erythematous plaques with or without edema If the condition becomes more pronounced, multiple areas of folliculitis may develop

5 Impetiginized plaques, the crust covering stumps

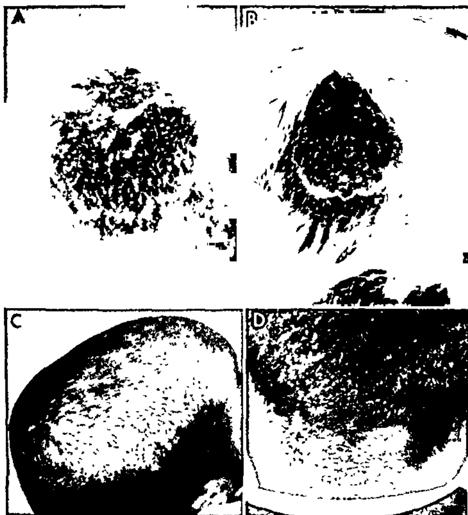
6 Kerion, often beginning as distinct nodosities and later forming boggy masses as coalescence occurs.

7 Lupus erythematosus-like, simulating either the early erythematous scaling or having a striking resemblance to the late form, with atrophy, scarring, and telangiectasis *Black dots at the border may mimic the follicular plugging of lupus erythematosus*

In all these varied clinical pictures, infected stubs which may break off at the surface of the scalp (black dots) are to be found unless only sequelae of the disease are present

The fingernails may become involved, and this infection resembles closely the nail disorder caused by T rubrum Pipkin found the nails infected in 25 per cent of his adult cases and 18 per cent of the adolescents having the scalp disease

When the glabrous skin is affected, circinate or gyrate lesions may form. Pipkin found that 59 per cent of adults having the scalp disease also had glabrous skin involvement, in the adolescent group 50 per cent had infections of both scalp and smooth skin. Trichophytid secondary to a glabrous skin infection was reported by Slaughter and Cawley.


A
B
C
D

DIFFERENTIAL DIAGNOSIS

It is probable that few dermatologists would misinterpret those instances in which there is patchy loss of hair. The cases of seborrheic-like scaling, particularly in adults, are the most difficult to recognize. At times the inflammatory features suggest impetigo, folliculitis, dissecting cellulitis, lupus erythematosus, and, of course, a mycosis caused by one of the other dermatophytes. This scalp disease should be suspected in both children and adults if there is a scalp disorder present which has not responded to treatment. Careful examination will reveal stubby hairs; often these are few in number.

One may be further suspicious of this disease if the patient has resided in Puerto Rico, in Mexico, or in southwestern United States.

Both the nail and the glabrous skin involvement should suggest fungous disease and should also invite careful inspection of other vulnerable tissues Absence from the feet of lesions suggesting T. rubrum may be helpful.

It is obvious but it may be repeated that one is not on sound ground unless all suspicious lesions are investigated by laboratory methods

PATHOGENESIS

According to Howell, Wilson, and Caro there are three stages in the invasion of T. tonsurans in the scalp:

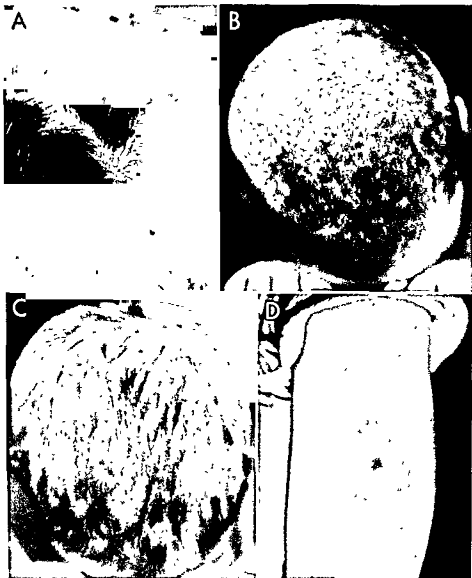
1. Epidermal phase.—In this phase the fungus spreads through the stratum corneum, eliciting a reaction in the skin which produces the clinical features of seborrheic dermatitis

2. Follicular invasive phase —The infection progresses continuously from the epidermis to the follicle and thence to the hair shaft and root. The cortex of the hair is invaded, the invasion resulting in fracture. Perifollicular inflammation can be demonstrated

3. Healing phase.—Healing occurs after extrusion of the infected hair Replacement of hair begins after several weeks unless atrophy has occurred Atrophy is seen only in cases of deep secondary pyogenic infection (kerion)

HISTOPATHOLOGY

Biopsy material removed from diseased tissue was studied by Howell, Wilson, and Caro In the type resembling lupus erythematosus, the findings were dissimilar from the findings in that disease Areas of parakeratosis in the scale, active acanthosis of the rete pegs, intracellular and intercellular edema throughout all layers of the epidermis, and a great number of plasma cells and polymorphonuclear leukocytes in the infiltrate were the chief distinguishing features


A
B
C
D

[illegible]

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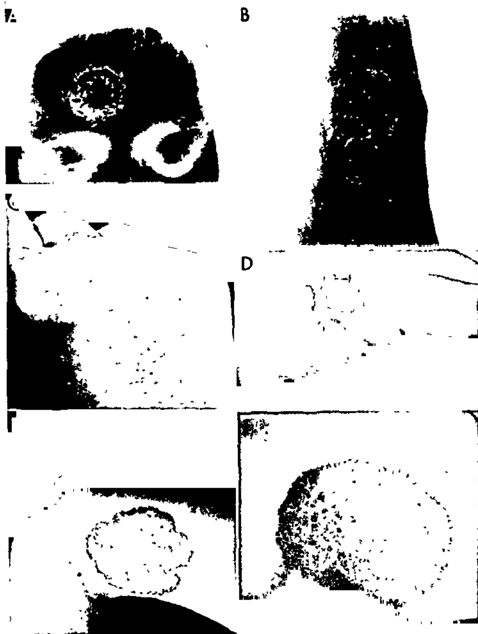


Fig. ?? [illegible]
clearir
there
hand
redness but being firmness

MYCOLOGY

1. Direct examination —The infected hair shows invasion of the shaft, with large spores in linear arrangement. No air bubbles are seen. Scrapings from the invaded skin and nails contain chains of spores.

2. Cultural characteristics.—There are several variants, formerly described as T crateriforme, T. cerebriforme, T. sulfureum, and T. acuminatum. Growth is moderate to slow. The colony remains compact and is usually limited in size Gradually the surface configuration becomes apparent and may be predominantly a central sharp-pointed umbo, an over-all convoluted effect, a crater-like central depression, or radial furrows. Some colonies exhibit more than one of these features. The color also is variable. The variant which develops a central depression is often creamy-white except for the crater, which is yellow. Other growths assume a sulfur-yellow hue, while red or brown tones are not unknown The undersurface of the colony is discolored reddish brown. Reports by Sullivan, Bereston, and Wood, as well as by Swartz and Georg, show that most strains require thiamine for good growth; an organic nitrogen was found preferable to ammonium nitrate.

3 Culture mount.—Microconidia, larger than those in Microsporum infection, are plentiful, being on short sterigmata and occasionally *en grappes* Chlamydospores may be seen With some strains occasional fuseaux are present

4 Biopsy of culture.—When cultures having the gross characteristics of *T. crateriforme, T cerebriforme, T. sulfureum, and T. acuminatum* are sectioned, there are minor variations within a pattern that is remarkably constant The fringe is often wide, depending on the degree of fluffiness of the surface. It consists of coarse hyphae in a loose network. Chlamydospores and microspores in abundance are also present The core is composed predominantly of tightly packed coarse mycelium. In older specimens there is a considerable component of round cells considered to be cross sections of hyphae or intercalary chlamydospores With higher magnification, racquet mycelium is occasionally observed There are relatively few filaments in the substrate

5 Filtered ultraviolet rays —The usual bright green fluorescence so typical of Microsporum-infected hairs is lacking when T tonsurans is the invader With dark hair no fluorescence will be observed However, in patients with light blond or gray hair, a pale-gray lusterless appearance may be seen under the Wood light In practice this would readily be missed unless the observer had devoted considerable time to study of the difference between this microorganism and suitable controls It is notable that the Wood light is of no help as a screening agent when this fungus is the possible etiologic agent

There is some variation in the appearance of fungus colonies under the Wood light This depends somewhat on the age of the growth but also

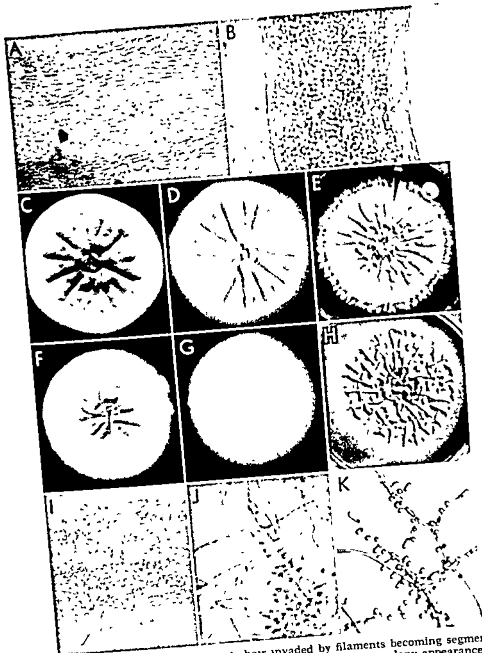


Fig 33 Trichophyton tonsurans A, hair invaded by filaments becoming segment … packed with spores, × 400 Gross colony appearance … red D flat with radial groo…

on the strain At first a lavender tone is common. Concentric bands may develop containing zones of greenish, brownish, or reddish hue. In older growths, an olive-green fluorescence is usually seen, being much more drab or subdued than the earlier colorations.

6. ANIMAL INOCULATION.—Guinea pigs may be infected, but the lesions heal spontaneously.

7. DIFFERENTIAL DIAGNOSIS (LABORATORY) —The absence of bright green fluorescence tends to rule out a Microsporum infection Direct examination of an infected hair reveals an endothrix Trichophyton. Absence of air bubbles is against T. schoenleini. T. violaceum is impossible to differentiate except by cultural studies

IMMUNOLOGY

The response to injections of trichophytin varies considerably In the inflammatory infections, the test is usually positive, and it is occasionally positive when the host response appears slight.

PROGNOSIS

There is not as much tendency to spontaneous cure at puberty as is evinced by Microsporum infections If untreated, the infection may last for many years The more primary the inflammation, the better the prognosis. Eradication of the disease requires meticulous attention to details

TREATMENT

Epilation by means of roentgen rays offers the best hope for cure of the scalp disease. The safeguards mentioned when this modality was discussed in relation to microsporosis (M audouini) should be meticulously followed It is even more important with T tonsurans infections to plan treatment carefully so that the patient is properly prepared prior to administration of the X rays and receives prolonged follow-up observation It is important that manual epilation of residual infected stubs be part of the aftercare following roentgen epilation

In those cases in which for one reason or another X-ray therapy is not considered desirab'e or is not available, the diligent application of local medicaments, accompanied by hand epilation of the visible crusts and stubs, proves effective in a percentage of patients that varies according to the author Pipkin stressed the need to pay meticulous attention to details, such as brushing in the medicament, removing loose hair, and always stroking in the direction of hair growth to lessen the likelihood of breaking off infected hairs Wilson has had good results from local application of Asterol dihydrochloride ointment 5 per cent The other available medicaments are mentioned in Chapter 2, "Microsporosis (Microsporum au-

10. Trichophytosis

(Trichophyton mentagrophytes)

ONE of the major types of superficial fungous disease, popularly known as dermatophytosis of the acute type, is trichophytosis (Trichophyton mentagrophytes). While it is predominantly an affection of the feet, hands, and nails, another form may involve other sites, including the scalp and beard It is now generally agreed that there is a fundamental relationship between the isolates of these diverse clinical disorders to establish this species as of uncommon interest to taxonomists

Synonymy: Trichophyton gypseum, Trichophyton interdigitale, Trichophyton niveum.

HISTORY

According to Ormsby, ringworm of the hands was noted by Tilbury Fox in 1870 and by Pellizari in 1888 The first detailed study of ringworm as it affects the hands and feet was that of Djelaleddin-Moukhtar in 1892, and credit should be given him for timely and accurate observations. Whitfield, Sabouraud, and Kaufman-Wolf made early reports.

In the United States, Ormsby and Mitchell were the first to report a comprehensive series of cases of ringworm of the hands and feet. Weidman's article (1927) was an important milestone in our knowledge. The literature on this subject was enriched by the exhaustive researches and careful, painstaking observations and deductions of J Gardner Hopkins and his group The studies were carried out from 1942 to 1945 at an infantry post, Fort Benning, Georgia

Allergic secondary lesions (dermatophytids) were described by Jadassohn and others of his school as emanating from a deep focus such as an infection of hair follicles C M Williams first showed that similar lesions can be present on a localized part of the body (usually the fingers and palms) when the primary focus is on the interdigital webs of the feet. This observation has been substantiated by Peck, Walthard, and many others

douini)," and are further discussed in Chapter 25. The observations of Pipkin point to a nail reservoir as important in spread of the infection. If fingernails are involved, surgical evulsion should be considered as the most certain rapid cure. (For technique, *see* Chapter 25, "Treatment of Superficial Mycoses.")

Lesions in the glabrous skin should be treated appropriately, milder concentrations being used when they are inflammatory and stronger ones if the clinical expression is less pronounced.

Obscure manifestations of the disease may be present in other members of the family or in close associates The physician should not neglect to examine all intimate contacts

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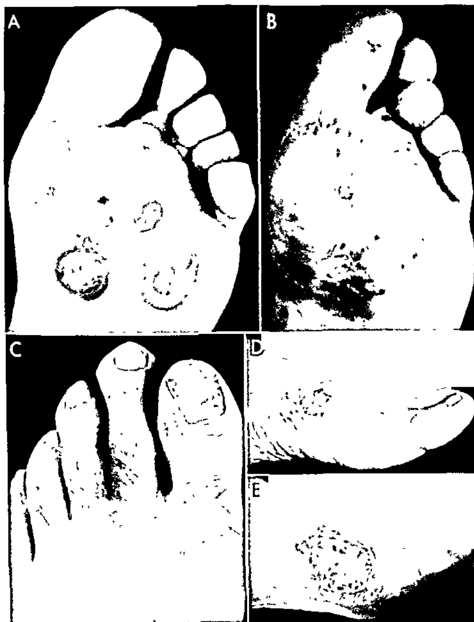


Fig 34 Trichophytosis (T. mentagrophytes). A, initial bullous lesions on sole B, spreading vesiculopustular eruptions over sole and toes C, scaly, inflammatory lesions on sides of toes and superficial and marginal invasion of nails of first two digits D and E, eczematous plaques extending to side of foot

ETIOLOGY

It has been variously estimated that from 50 to 90 per cent of the population of the United States have a dermatophytosis of some type at some time during their lives. Hulsey and Jordan recorded a clinical incidence for tinea pedis of 67 per cent and a microscopic incidence of 63 per cent in a series of 100 university students. Gilman noted that of 390 new patients with diseases of the skin seen during six months in the Student Health Service of the University of Pennsylvania, 145 (37 per cent) had a mycotic

TABLE 7.—RESULTS OF CULTURE OF MATERIAL FROM FEET OVER FIVE-YEAR PERIOD

ORGANISM	NO OF CASES	PERCENTAGE OF CASES	PERCENTAGE OF ORGANISMS
T mentagrophytes	247	30 4	47 4
T rubrum	217	26 7	41.7
E floccosum	35	4 3	6 7
C albicans	22	2 7	4 2
No growth	292	35 9	
Total	813	100 0	100 0

infection. The average age of these patients was 19½ years Gilman examined 500 students, 297 (60 per cent) had gross evidence of ringworm. Legge, Bonar, and Templeton found that 53 3 per cent of the men and 15.3 per cent of the women of the 3,100 freshmen in a university were infected and that at the end of the spring semester 78.6 per cent of the men and 17.3 per cent of the women had tinea pedis Muskatblit examined 112 medical students and 100 dispensary patients. Evidence of dermatophytosis was presented by 89 per cent Andrews and Birkman in a clinical study of 520 public school students between the ages of 14 and 20 noted that 65 (12 5 per cent) showed clinical signs of fungous disease We can substantiate the relative infrequency of Trichophyton infection in adolescents and in children Prehn found that 88 per cent of 1,500 men examined on 11 ships of the United States Navy showed clinical evidence of ringworm of the feet In a survey of over 300 patients in a home for the aged we found evidence of residual infection in the skin and nails of over 90 per cent, only a few of the patients complained of the condition Ajello, Keeney, and Broyles stated that 40 per cent of young men entering military life had normal feet, whereas for the troops at Fort Benning, Hopkins and his coworkers reported normal findings in only 20 per cent when the feet were examined painstakingly by clinical, microscopic, and cultural methods

From study of statistics it would appear that at least 50 per cent of all cases of dermatophytosis are caused by T mentagrophytes The incidence is higher in young adult life and lower with increasing age

The disorder is seen much oftener in males than in females This fact may be due in part to more particular hygiene on the part of women or to the greater chance of contamination on the part of men due to their greater

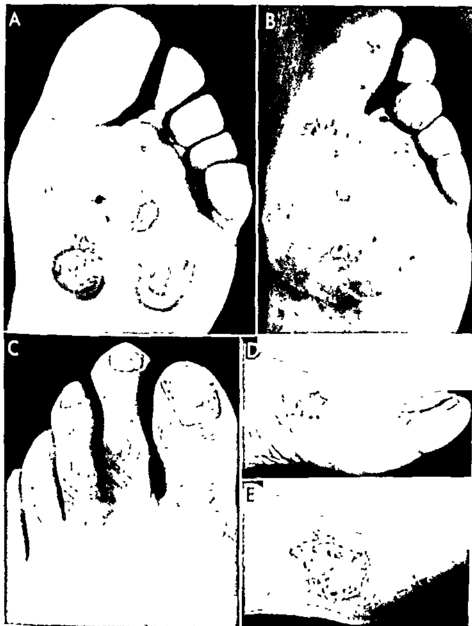


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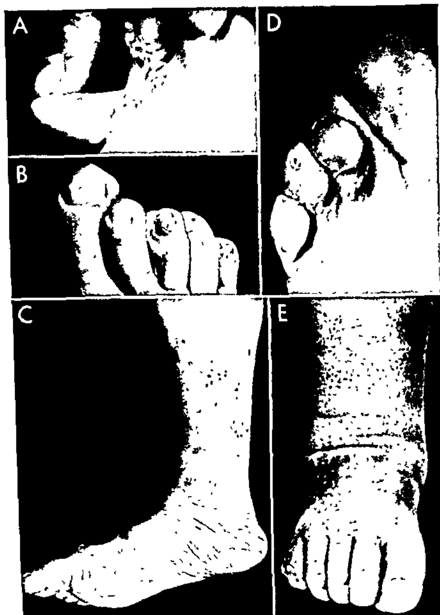


Fig 35 Trichophytosis (T. mentagrophytes) A, soggy, desquamative focus on web and sides of toes B, same patient, showing eroded, friable nail at site of contact with overlappir
patier
scaly,
toes
gitis, both T mentagrophytes and Streptococcus were isolated from interdigital webs.

interest in athletics and to their congregating in camps, clubs, and gymnasiums, with the common use of locker rooms, shower baths, and other facilities. There must be still another reason, since many wives who have been exposed prior to diagnosis of the condition fail to become infected It seems that men are more vulnerable. There was apparently a greater incidence of disabling dermatophytosis in the armed forces in World War II than in the same age group in civilian life. This observation is not unexpected, despite improved methods of therapy, for the troops walk in bare feet over floors bound to be infected, there is common use of bathrooms, hygiene is poor during combat service, and trauma and sweating after long marches are conducive.

The disease is more prevalent in the summer. We observe fewer cases in New York in the winter than in the summer, and the character of the disease varies considerably with the season. In summer, exceedingly acute involvement occurs more often, and there is generally more inflammation.

Hyperhidrosis is a common finding in patients with acute dermatophytosis. Just how much the sweat has to do with the furtherance of the infection has been the subject of study of a number of investigators Levin and Silvers showed that fungi will grow in sweat. Peck found that true sweat has fungistatic power not possessed by insensible perspiration. The latter, when present to excess, produces maceration of the skin, which accordingly is more vulnerable to the invasion of fungi. The alkalinity or acidity of the sweat may play a part in the predisposition to infection. The diet, the amount of sweat secreted, and the amount of evaporation are factors in the pH of sweat.

Lowering of a patient's vitality during a debilitating illness may be reflected in a predisposition to the disease. A quiescent interdigital infection may then become inflammatory and spread to adjacent and remote cutaneous areas.

In many instances, predisposing factors may not be manifest, and we are forced to conclude that infection may often take place when normal persons come in contact with pathogenic fungi An abrasion may provide a portal of entry, but even that is apparently unnecessary in most cases A major factor in the etiology and consequently in prophylaxis of the condition is determination of reservoirs in order that they may be avoided or eliminated The chief foci are to be found on the feet of carriers, who are unaware of the disease or are careless in treating it That pathogenic fungi may remain viable for some time in a dry state has been proved by Farley, Weidman, Mitchell, and others Weidman calculated that many pathogenic fungi may survive in the dry state from approximately six months to a year. Fungi of pathogenic titer have been yielded by cultures of material from floors, mats, and gymnasium apparatus (Williams), shoes (Jamieson and McCrea), cotton, linen, and silk (Hruszeck-Kadisch), wool and silk and many different woods in the presence of moisture (Bonar and Dreyer), and dry horse dung (Muende and Webb) Goldman mentioned that spores

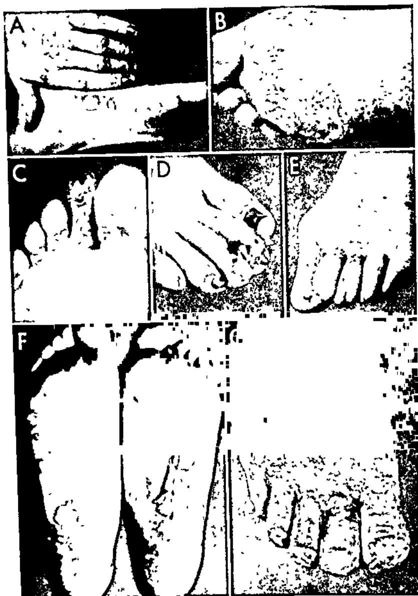


Fig. 36. Trichophytosis (T. mentagrophytes). A, maceration on the interdigital webs of the feet and vesicular rash on the sole and hands (no fungi discovered), considered a good example of dermatophytid B, erythematous, squamous eruption suggestive of

of fungi have been carried nearly 14 miles (22 kilometers) into the stratosphere and have survived cold, solar radiations, and other extreme conditions. Fortunately, however, the spores of fungi are not as resistant as those of bacteria Moreover, they are readily destroyed by heat. Weidman found that most species of fungi in culture and in scrapings were killed by exposure to a temperature of 48 C for 10 minutes.

While unusual, the possibility of acquiring the disease from a laboratory animal must be kept in mind. Booth reported an epizootic of T. mentagrophytes infection of white mice, with transmission of the disease to a laboratory worker. Fuentes and Aboulafia isolated T. mentagrophytes from 15 of 113 adult guinea pigs clinically free of ringworm infection. This fungus has also been isolated from a normal cat by Fuentes, Bosch, and Boudet. A variety of domestic, captive, and wild animals may harbor this fungus, often without clinical evidence of disease. Infection in rural areas may be transmitted by spores or infected hairs shed by rodents (Georg).

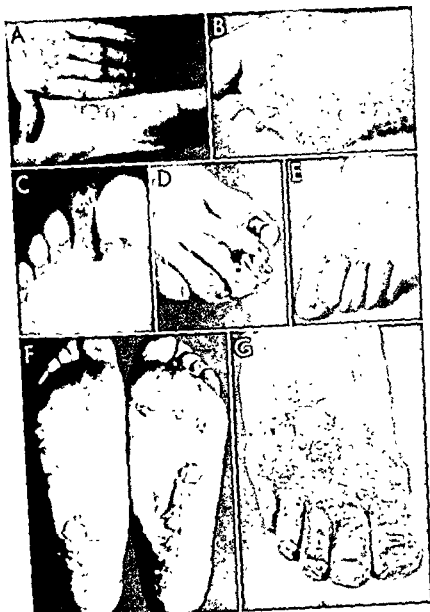
CLINICAL CHARACTERISTICS

T mentagrophytes is the cause of most of the inflammatory intertriginous and spreading fungus infections of the feet. The toenails are also commonly affected, and rarely one or more fingernails is involved. Other intertriginous parts of the body, such as the groin and the axilla, may become the seat of the disease Trichophytids produced from intertriginous foci are often part of the syndrome. The downy types rarely affect hair follicles, the granular or powdery varieties may produce acutely inflammatory follicular infections of the scalp and other parts of the body. T mentagrophytes is one of the causes of kerion

1 Involvement of skin —The disease commonly makes its appearance on the feet in the form of vesicles on an interdigital web, on the sole, or on both.

In the first-mentioned location the vesicles, or bullae, rupture readily, and the skin at the site of the lesion becomes macerated and soggy The process is usually associated with a certain degree of erythema, but this may be lacking The condition may remain in this stage for weeks, months, or years On examination some maceration and peeling may be noted The development of fissures or cracks is common. For some reason not yet known, the web between the fourth and the fifth toe is particularly vulnerable In this stage the inflammatory form may be indistinguishable from the chronic type (due to T rubrum)

With favorable conditions the disease may assume a more inflammatory character This change occurs usually although not exclusively during the summer season The first indication may be pruritus of the toes accompanied by some swelling and followed by the appearance of vesicles. The soles may be the chief areas affected, but if the inflammation is violent, vesicles may appear on the sides of the toes and feet. Owing to



[illegible] A maceration on the interdigital webs of [illegible]

scratching and irritation from local applications (self-medication being exceedingly *common*), *there is an increase in the inflammatory reaction*, and secondary pyogenic infection may appear. Coincidentally with the increase in the local inflammation on the feet and frequently with the development of lesions on the soles, vesicles may appear at a site or sites remote from the original infection. The hands (particularly the palms and sides of the fingers) are chiefly affected This type of eruption is due to the dissemination of products of fungi through the blood stream, and the lesions are known as dermatophytids. Because of mismanagement, a low state of resistance, or a virulent strain of organism, the condition may spread from the feet to involvement of contiguous areas, sometimes of wide extent. The eruption is erythematous and vesicular in patches and is fairly well demarcated from normal skin. The folds and intertriginous areas are most vulnerable, and the infection may spread to any or all of the following sites. the upper parts of the thighs, the perianal region, the umbilicus, the axillae, and the inframammary regions. There are instances of primary involvement of the hands and of other parts of the body. With acute inflammation, secondary pyogenic invasion of the tissues is common. At times the pyogenic element overshadows the characteristics of fungus disease. If the process becomes frankly pyogenic and spreads, the disease may have changed to infectious eczematoid dermatitis. Many clinicians believe that eczematous eruptions on the hands or elsewhere may be of fungus origin but persist owing to coincidental sensitizations or secondary pyogenic involvement It is our opinion that fungous disease predisposes to contact sensitivity, so that a patient who ordinarily is not reactive to soap, dyes, salicylic acid, and so on may develop an inflammatory response to these or to many other drugs or chemicals and that the superadded insult to the skin is often important in accounting for the lack of response of the disorder to therapy

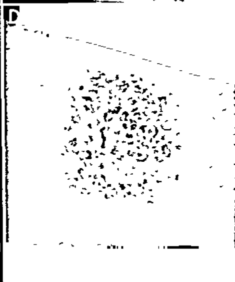
Sanderson and Sloper examined 1,424 men in the British Army serving in Malaya and Hong Kong and found 33 5 per cent suffering from body ringworm due usually to *T mentagrophytes* The lesions were crural, scaly circinate plaques or, in hairy regions, deep, follicular and purulent. It was not unusual to see 20 to 30 lesions The authors concluded that such lesions were often acquired from the patient's own feet. The skin condition popularly known as "jungle rot," which was observed commonly in the South Pacific during World War II, is essentially a *T mentagrophytes* infection with the complications mentioned, abetted by the hot, humid climate

2 Involvement of nails —As part of the process, the nails, particularly of the toes, are not uncommonly affected In fact, nail tissue may be the first to be involved The infection with *T mentagrophytes* may be superficial, merely causing a white patch on the surface or in the substance of the affected nail (leukonychia trichophytica) Or there may be a more inflammatory and destructive involvement, in which case the nail becomes









[illegible]
fecting microorganism

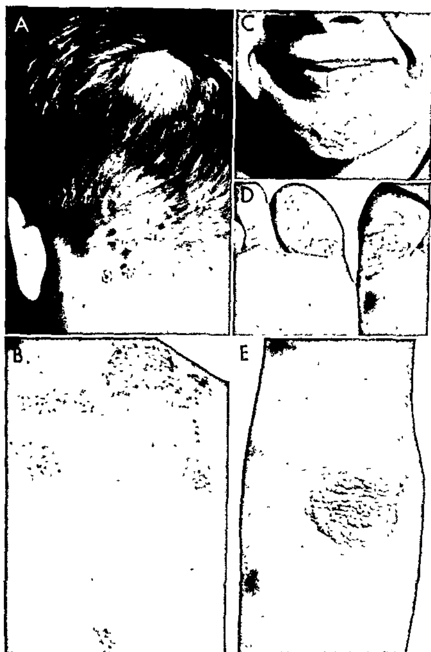


Fig 38. Trichophytosis (T. mentagrophytes). Family infection showing variations in site of involvement and in degree of inflammation Source of infection was not determined All three patients responded readily to therapy Culture in each case revealed granular type of T mentagrophytes **A,** pustular scalp infection of one month's duration in boy aged 5, **B,** glabrous (eczematous) lesions of two weeks' duration in girl aged 4 **C, D,** and **E,** involvement of face, toes, and right elbow of one year's duration in boy aged 8, in all sites lesions showed mild inflammation

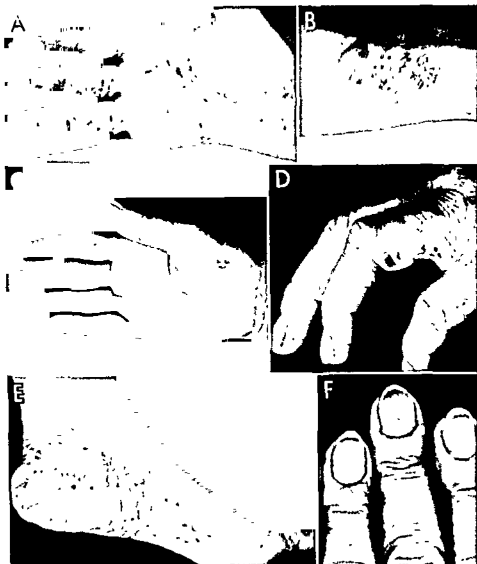


Fig 39. Trichophytosis (T mentagrophytes). There may be focus on webs of feet or elsewhere, or infection may be primary Dissemination may take place externally or [illegible]

resembled dysidrosis F, early involvement of nails showing destruction and separation at base, violence of process produced spontaneous cure, and new nails were normal

site. The resemblance to kerion, as noted in the case of ringworm of the scalp, is frequently striking. Hairs in the affected tissue loosen and either come out spontaneously or are readily extracted.

5. DERMATOPHYTID.—This subject was briefly considered in the paragraph on involvement of the skin and was also discussed in Chapter 3, "Microsporosis (Microsporum Canis)" The term dermatophytid is probably better than trichophytid, since allergic rashes due to Microsporum may be clinically indistinguishable from those due to Trichophyton. Guth, Bloch, W. Jadassohn, Peck, and others have contributed to our concept of these rashes. It has been stressed by Bloch, Jadassohn, and their school that allergy or an acquired specific sensitization is an invariable accompaniment of the rash The eruption was at first thought to follow only kerion, being caused by dissemination of the products of fungi through the blood stream. Williams was the first to show that secondary eruptions may follow infection of the interdigital webs, and he later reported that macerated tissue in the groin may act in a similar way as the focus for a secondary rash at a remote point The suggestion that nails may act in like manner as a focus for dissemination of the products of fungi through the blood stream has not been confirmed.

The term dermatophytid (or trichophytid) appears to have been considerably overworked in this country. It is used by many without any tangible evidence to account for the erythematous, vesicular, and eczematous eruptions which so commonly affect the hands. We believe that a diagnosis of dermatophytid should be arrived at only after careful observation and study There are definite criteria which must be fulfilled before this diagnosis is acceptable. Peck has laid down theoretically sound rules. His dictum that a positive blood culture is essential is perhaps too drastic. The following conditions for the diagnosis of dermatophytid, however, are minimal and also obligatory.

(*a*) There must be a demonstrable focus, and this focus must contain pathogenic fungi On the feet, in the majority of instances, the causative fungus is T mentagrophytes We have never observed dermatophytid with T rubrum infection

(*b*) The secondary rash may appear after irritation of the primary focus by treatment or after a spontaneous inflammatory change

(*c*) The intracutaneous test with trichophytin reveals a positive reaction at the test site The type of response is dependent on the type of dermatophytid

(*d*) Fungi are usually not found in the lesions of dermatophytid

(*e*) The rash disappears spontaneously when the focus has been eradicated The only exceptions occur when there are secondary eczematous changes and the rash continues because of sensitivity to other substances or because of the action of primary irritants

The following clinical types of dermatophytid are observed

(*a*) *Lichenoid and urticarial* —In the classic dermatophytid following

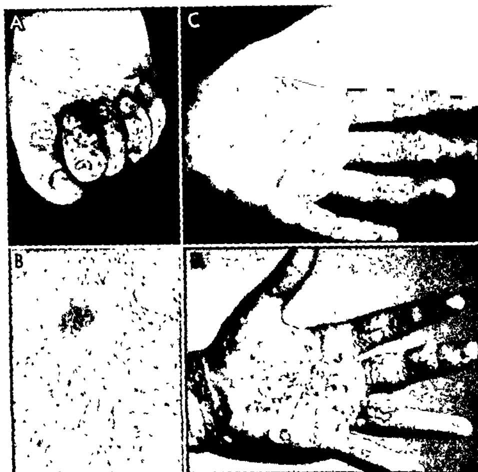


Fig 42. Trichophytosis (T mentagrophytes) A, acute inflammatory reaction of foot increased from ill-advised irritating topical applications B, delayed tuberculin type response to intradermal injection of trichophytin, after one week C, dermatophytid of dry type (keratosis exfoliativa) secondary to acute infection of feet D, vesiculopustular dermatophytid, primary focus being on feet Palms and sides of fingers are sites of election

a deep infection of hair follicles, the trunk is usually involved The character of the rash varies considerably. Follicular localization of lichenoid papules is common, but eruptions simulating erythema toxicum are also observed Headache, mild fever, and malaise are frequently present.

(*b*) *Vesicular.*—With the dermatophytid described by Williams there is a tendency to a localized rash, the sides of the fingers and the palms usually being the sites. The reason for this localization is not known. The terminal circulation of the hands, traumatic factors, contact with fungi producing local sensitization, and sensitization to light have been considered. It is not by any means a unique experience in dermatology to be unable to explain the localization of a disease process, no one has satisfactorily explained the frequent involvement of the knees and elbows in psoriasis. The lesions are essentially vesicular, being similar in appearance to dyshidrosis, although the contents frequently become purulent Constitutional symptoms, often associated with dermatophytids secondary to kerion, are not commonly seen.

In all cases, even if the appearance of the rash and the results of the investigation point to dermatophytid, possible sensitization from external contacts should be considered, and patch testing with suspected substances is always in order.

The same type of vesicular dermatophytid which appears on the hands may also be found on the feet, particularly on the soles. Here, as on the hands, examination for fungi may yield negative findings

(*c*) *Keratolysis exfoliativa.*—The condition known as keratolysis exfoliativa was studied by MacKee and Lewis, who considered that it is often a form of dermatophytid They found that it frequently occurred in patients who had an active mycosis of the feet and that vesicular dermatophytids were commonly present In keratolysis exfoliativa the lesions consist of superficial scaly macules, which may coalesce and are localized to the palms and/or soles The lesions at first are unruptured empty vesicles The scale is as thin as cigarette paper When it is broken, collarettes are formed at the edges Only a few lesions may develop, or most of the skin on the palms and soles may be affected. The almost constant presence of the mosaic fungus was considered significant but is disputed by many

(*d*) *Erysipelas-like* —Another type of dermatophytid occurring on the legs has been described as erysipelas-like It appears to be proved that in some of the reported cases secondary allergic lesions arose from a focus on the interdigital webs of the feet Waisman was able to reproduce this manifestation by injecting trichophytin at the site In other cases, little proof was offered that the lesions were not in reality of streptococcic origin In several instances of eruptions of this character, with localized erythema and swelling and sometimes with fever and prostration, fungi were demonstrated in scrapings from the feet. The trichophytin test, however, did not elicit a positive reaction in every case, even when a site near the lesion was tested. Furthermore, in a number of instances bacteriologic studies re-

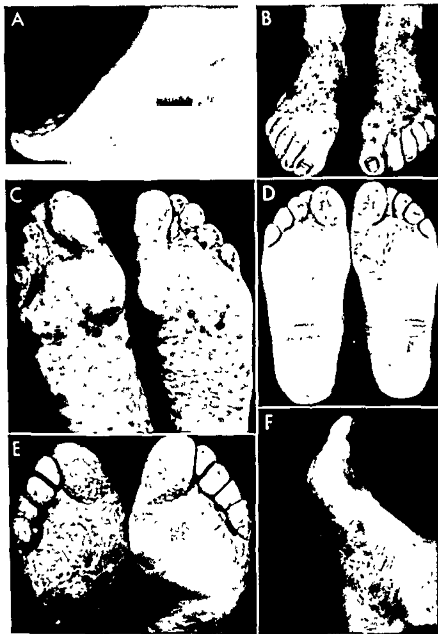


Fig 43 Nonmycotic diseases simulating fungus disease caused by T. mentagrophytes. A, contact dermatitis from vegetation **B,** pyogenic eczema **C,** secondary syphilis with maculopapular lesions on soles and moist, eroded lesions on webs and undersurfaces of toes **D,** contact dermatitis from thermoplastic material in shoe **E,** psoriasis **F,** pustular psoriasis (**C,** *courtesy of Dr Royal Montgomery*)

vealed the presence of Streptococcus. Further study appears to be necessary to prove beyond doubt that in all or in most of these cases the condition is due entirely to the dissemination of fungi from the focus on the feet.

(e) *Erythema annulare centrifugum.*—Jillson and Hockelman have offered good evidence that in some instances this disease represents a dermatophytid. Besides the fact that it fulfills the usual criteria, Jillson found that one week after trichophytin was injected both within and outside a lesion, the inner site was represented by a fading macule, whereas the reacting site outside the lesion had enlarged to produce a miniature replica of erythema annulare centrifugum

DIFFERENTIAL DIAGNOSIS

1 Interdigital lesions.—If the infection is present only on the interdigital webs of the feet, it may be impossible to determine the species of infecting microorganism by clinical observation. If all the webs are affected, infection with C. albicans is probable. The bright-red base and overhanging collarette of skin suggests moniliasis. Intertrigo caused by T. rubrum or by T. mentagrophytes may be indistinguishable. There are a number of instances of failure to demonstrate a pathogenic fungus In some of these cases certain bacteria, especially strains of hemolytic Streptococci, have come under suspicion without decision

Scaling between the toes due to the injudicious use of strong chemicals may lead the physician astray. Several instances of this character have come under our observation. The lack of laboratory confirmation and healing under bland applications tend to rule out tinea pedis. Maceration of the interdigital webs without evidence of inflammation may be caused by increased perspiration or by lack of drying after the bath. Moist tissue is

suspicious, and examination for condylomas or other evidence of the infection will be fruitful

Soft corns are not uncommon and may be found in association with a fungous infection They are, however, caused not by a fungus but by pressure of ill-fitting shoes When they are present at the base of the web they may on superficial examination suggest tinea pedis

2 Acute inflammatory tinea pedis —Acute tinea of the feet, caused most commonly by T mentagrophytes, is usually accompanied by interdigital maceration It should be remembered, however, that inflammation of the foot and tinea of the webs may be unrelated disorders In most cases of inflammatory tinea the reaction to the trichophytin test is positive

A patient may present soggy, thickened, honeycombed soles, most involved over points of pressure The odor is that of dirty feet Although this condition is almost invariably attributed to fungous infection, the results of

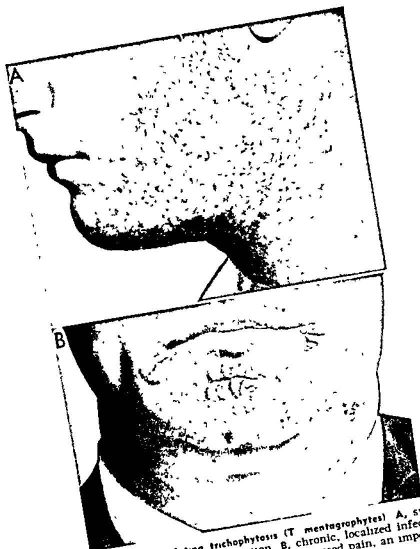


Fig 44 Pyoderma simulating trichophytosis (T mentagrophytes) A, sycosi showing diffuse follicular pustular eruption B, chronic, localized infection area were firmly attached and attempts to epilate caused pain, an importa differentiating condition from fungous disease

culture are usually negative. It is our opinion that hyperhidrosis plus bacterial invasion is responsible.

Dermatitis venenata due to sensitivity to shoe leather, to the dye in stockings, to foot powder, and to corn cures and the like should be considered when the inflammatory disorder is limited at first to the region of the contacted substance. Once this dermatitis is established, secondary eczematous changes may quickly occur, confusing the picture. The lack of other evidence of fungous disease, the negative findings on mycologic examination, the results of patch testing, and cure when the offending article is eliminated from the environment of the patient aid in establishing the correct diagnosis.

3 SCALP AND BEARD.—The history of contact with an infected animal or with a human infection makes for an easy diagnosis. Differentiation from other fungous infections on clinical grounds may not be easy if the presenting lesion is a kerion In such instances the laboratory findings will be decisive. In pyoderma of the sycosis type, epilation in the area is painful and difficult to accomplish Dissecting cellulitis of the scalp has a tendency to spread and affect multiple sites, which is not characteristic of kerion

4. DERMATOPHYTID-LIKE ERUPTION —Toxic eruptions simulating dermatophytid may result from sensitivity to certain drugs. The absence of signs of a focus of tinea, the lack of an inflammatory focus on the feet, and the history of ingestion of a drug point to the correct diagnosis When a vesicular eruption is present on the hands, particularly on the fingers and palms, the diagnosis of dermatophytid is commonly given, even without corroboration In the majority of such cases, however, the condition is not of fungous origin The criteria for the diagnosis of dermatophytid have already been detailed, it is at least necessary to find an active fungous focus and to observe a positive reaction to the trichophytin test The diagnosis of dyshidrosis, or pompholyx, is made by excluding dermatophytid and dermatitis venenata The former disorder has been discussed, in diagnosing the latter, one is helped by the absence of an active fungous focus and of a *reaction to trichophytin, but their presence does not exclude the condition* An accurate history of contact with a possible sensitizing agent, particularly if the initial exposure was fairly recent, may point to the correct diagnosis. When secondary eczematous changes result from trauma or misdirected therapy, an additional factor or factors may make a definite diagnosis impossible Unfortunately, a large number of patients with such lesions present themselves for treatment, they constitute a rather unsatisfactory group, in regard to both accurate diagnosis and therapeutic results We believe that it is a mistake to classify all eczematous changes on the hands as dermatophytids

When part of a widespread eczematous condition, whether due to contact or to some other cause, involvement of the feet or ankles may mislead the unwary physician He may consider the whole eruption mycotic be-

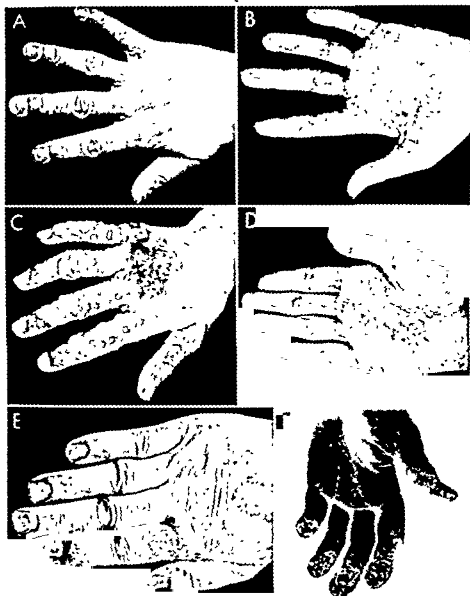


Fig 45. Nonmycotic rashes simulating trichophytosis (T mentagrophytes) A, erythema toxicum B, contact dermatitis C, erythema multiforme D, psoriasiform eczema E, nummular eczema F, dermatitis repens

culture are usually negative. It is our opinion that hyperhidrosis plus bacterial invasion is responsible.

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change may also be apparent in circumscribed sectors. If material from two sectors is transplanted, the character of each sector is retained. Besides the type usually isolated, we recognize three types which are probably derivatives or at least closely related: (1) a granular type, (2) a white fluffy growth (T. interdigitale), and (3) a white compact growth (T. niveum). In addition to the interchanging types of growth (granular or fluffy) which have been noted at different times in cultures of material from the same infection, other evidence has accumulated that the types of T. mentagrophytes mentioned here are closely related. The pigmentation in the subsurface portion of the colony is similar in all types, provided the same batch of dextrose agar is used. This is characteristically a dull rose-tan.

1. MICROSCOPIC FEATURES.—T. mentagrophytes is an ectothrix Trichophyton; the fungus is external to the hair, and the spores tend to form chains The spores are similar in size to those of the Microspora. In scales, macerated skin, and nail tissue the organisms appear as chains of spores or as segmented mycelium with little branching

2. CULTURAL CHARACTERISTICS.—(*a*) The type usually isolated appears first as a white and fluffy growth. After 10 days to two weeks the surface becomes velvety, flat, and light buff or buff-yellow. There is usually a boss at the center, and occasionally there are a few irregular folds (*b*) The granular or powdery type of growth is characterized by its powdery or velvety surface, stellate or denticulate margin, and fluffy changes developing as it ages The color is light buff or maize-yellow. The rate of growth is moderately fast. (*c*) The white fluffy type of culture (T. interdigitale) begins as a downy, feather-like projection; the growth develops rapidly and within two weeks almost covers an agar slant. It is almost pure white. The growth shows many aerial hyphae. (*d*) The white compact type (T. niveum) at first grows out white and fluffy The surface then becomes compact, and irregular elevations and depressions make their appearance. The snow-white color is retained A rose-colored velvety or powdery variety is also occasionally seen.

3 CULTURE MOUNT.—(1) The ordinary type is characterized by spirals. Fuseaux with blunt ends are present in small numbers. Nodular organs, pectinate bodies, racquet mycelium, and chlamydospores are also to be noted The mycelium is septate and usually branched Microconidia are to be seen as thyrsi and as *grappes*. (2) The granular type shows few spirals There are numerous blunt-end fuseaux with dense masses of microconidia produced in *grappes* and thyrsi. Chlamydospores and racquet mycelium are present in the subsurface growth (3) In the fluffy type (T. interdigitale) the aerial growth contains a large percentage of vegetative filaments There are limited numbers of microconidia in small clusters. Nodular organs and racquet mycelium may be found. Spirals and fuseaux are usually absent (4) In the white compact type (T. niveum) the findings are essentially the same as in the fluffy type.

4. BIOPSY OF CULTURE.—In the fluffy type the fringe is wide and con-

cause the feet are involved. If the trichophytin reaction is negative, the diagnosis of tinea may be excluded.

The disease known as pustular psoriasis or pustular bacterid frequently presents a confusing picture. The lesions appear in groups of small, thick-walled pustules. The arch and the heel are the commonest locations on the foot, but lesions may develop elsewhere. Frequently the hands are concomitantly involved. The lesions are usually sterile. Barber, Andrews, Hopkins, and others have observed that in such cases cure has resulted from the removal of foci of infection. The resemblance to tinea pedis may be striking, but lack of interdigital localization, resistance to therapy, and lack of mycologic confirmation should be sufficient to indicate the correct diagnosis.

With acrodermatitis perstans or dermatitis repens, which are similar if not identical disorders, the initial lesion is usually paronychia From this arises an undermining pustular eruption, which spreads on one digit and may finally involve large sheets of skin. If the condition is untreated, an exudative eczematous process ultimately develops.

Streptococcic infections have been credited by Mitchell with causing lesions on the feet which resemble those due to fungi.

Nummular eczema is superficial, does not show a tendency to central clearing, and does not respond to the usual fungicides. Results of all laboratory examinations are negative.

PATHOLOGY

The changes in acute dermatophytosis are similar to those observed in acute eczematous eruptions The stratum corneum shows some parakeratosis. Small vesicles are to be seen below this layer. The intensity of the process determines the degree and extent of vascular dilatation, of edema, and of round cell infiltration in the upper cutis In other words, there is a superficial exudative inflammatory process with some epidermal (eczematous) changes

MYCOLOGY

It should be noted that T. mentagrophytes is unstable and given to the development of variants It is by no means certain that placing together the various growths in this one species is the final solution Many workers consider T interdigitale (Kaufman-Wolf) to be a pleomorphic form Silva and Benham and Georg, from investigative studies, came to agree with the time-honored concept that the more granular the colonies, the more virulent the clinical expression Weidman observed a periodic transition from a fluffy to a powdery and back again to a fluffy condition in a growth isolated from his own toes We have observed that when a granular form of T. mentagrophytes is subcultured it tends to become more fluffy This

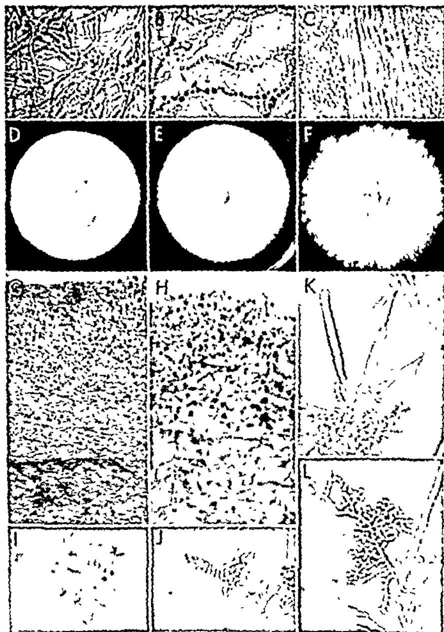


Fig 46 *Trichophyton mentagrophytes* A, profuse network of filaments in specimen

sists of a loose network of hyphae with many microspores. In the granular type, the fringe consists predominantly of microconidia, many in clusters. Some spirals are observed. The core is well defined above and below, it consists of filaments, and on higher magnification chlamydospores are often noted. In the substrate the filaments are fine, with a tendency in some specimens toward linear direction. Nodular organs may be seen in the fluffy variety.

5. FILTERED ULTRAVIOLET RAYS.—No fluorescence is detected when follicular infections caused by ectothrix Trichophyta are examined under filtered ultraviolet rays. Fungi in nails, scales, or macerated tissue do not show any fluorescence. In culture, the granular type is typically bright and clear and shows concentric bands of color, beginning with a light soft blue-violet in the center. The edge is fawn colored. With the compact and fluffy types the color of the entire colony is bright, indistinct mauve. The T. niveum type has a yellow tone throughout.

6. ANIMAL INOCULATION.—The granular type of organism is inoculable into guinea pigs, dogs, cats, and rabbits. The fluffy types have probably lost their pathogenicity for these animals

7. DIFFERENTIAL DIAGNOSIS (LABORATORY).—When T. mentagrophytes invades a hair follicle, it produces considerable inflammation. The hairs are not broken, but they may lack color The fungi are not found in the shaft The spores are in linear formation and sparse, in contrast to those of species of Microsporum. In examination of scales and macerated tissue it is difficult and at times impossible to determine species. On culture, T rubrum must be differentiated The initiation of growth is faster in all types of T mentagrophytes. In the ordinary type of T. mentagrophytes the central fluffy portion is smaller than it is in T. rubrum. In the fluffy type of T mentagrophytes the aerial hyphae are most luxuriant, often being present on the sides of the tube The fluffy form of T rubrum grows up in a hemispheric mass but is never seen along the test tube The color of the pigment is different in T rubrum and in T mentagrophytes. In the former it appears earlier and is deep rose-purple In the latter, the color is seen in older colonies and is dull rose-tan The difference between culture mounts of these two species is frequently difficult to determine. In T. rubrum we have never seen spirals and have noted few fuseaux In culture biopsy of the fluffy type, the fringe shows numerous microconidia enmeshed with hyphae, and spirals may also be present The fringe of the granular variety reveals predominantly clusters of microconidia. The core is well demarcated and dense Occasional nodular organs may be found in the substrate

IMMUNOLOGY

Patients who show primary inflammatory reaction to this fungus also react to trichophytin It is our experience that the powdery type sensitizes

(*b*) *Vesicular lesions on soles accompanying interdigital maceration.* —Multiple procedures may be employed: a foot bath with hot boric acid solution for one-half hour morning and night; topical application at bedtime of a preparation such as 1 per cent tincture of iodine, and liberal dusting with a boric acid foot powder in the morning. Such treatment is [illegible]

Chapters 2 and 25 It is important to prescribe only drugs which the physician knows will not aggravate the problem. In other words, good judgment on the part of the physician is required. One is better advised to use remedies with which he is familiar than to experiment with something built up by promotion and hearsay.

(*c*) *Overtreatment dermatitis complicating tinea of feet and hands.*—This is commonly encountered. The object of therapy is to treat the dermatitis and not to employ any fungistatic preparation that might further irritate the skin If the eczematous lesions are exudative, a mild wet dressing or bath may be employed Use of either normal saline or boric acid solution is suitable and may be the principal procedure. For effectiveness the solution must be used for at least one-half hour four times daily and in some instances more frequently or for longer periods. Two other remedies may be considered: An ointment such as Lassar paste may be applied at bedtime and left on overnight if the exudation is not too copious, and a 3 per cent boric acid powder may be dusted on the affected skin after the soaks. Good results usually require several days of faithful persistence. It is not desirable to abandon such mild remedies to experiment with potentially irritating drugs which could not possibly help. Dermatologists sometimes administer mild doses of X rays to the inflamed skin If pruritus is a troublesome symptom, one may prescribe an antihistamine drug such as tripelennamine (Pyribenzamine), 50 mg. three times daily after meals, or chlorpheniramine (Chlor-Trimeton), 4 mg four times daily after meals and at bedtime

(*d*) *Pyogenic complications* —One must be alert to this possibility. If pustules and spreading pyoderma supervene, hot wet packs of boric acid [illegible]

avoided because of the possibility of species reaction with flare of the active disease

(*e*) *Trichophytid* —While in theory the vesicular lesions on the fingers [illegible]

usually well tolerated in the uncomplicated case if applied only once daily. If there is considerable associated edema or exudation, wet packs of saline or boric acid solution are indicated

the skin to a greater degree than the fluffy type and that allergic reactions (ids) are commoner with the powdery type.

PROGNOSIS

If well managed, most patients respond satisfactorily within a few weeks. Infections of long standing, particularly when overtreatment dermatitis is present or when the disease has become extensive through neglect, are much less responsive and may require careful and prolonged treatment. Inability to prevent hyperhidrosis or to rest create less favorable situations. A vigorous reaction to the trichophytin test is a hopeful sign.

TREATMENT

At all times there is the tendency for an inflammatory reaction to develop, and this should be kept in mind in deciding what type of therapy to advise The infection is exceedingly easy to overtreat. Avoidance of contact with irritants, such as soap, and of friction from shoes, as well as trauma from scratching, should be emphasized. The trichophytin test may provide further information of value, as a strongly positive reaction shows an innate ability to develop an inflammation at sites of contact between fungus and skin. While it is never easy for a patient to interrupt his work, bed rest is sometimes required This accomplishes two things; it eliminates irritation and allows the affected skin to be treated with wet dressings. As an adjunct to other procedures, bullae may be incised or clipped away. An effective systemic antibiotic against *T. mentagrophytes* is not available Physical agents, such as X radiation, have limited nonspecific value in helping to lessen inflammation. The administration of ultraviolet rays is contraindicated

1. TRICHOPHYTIN.—The only other remedy to be mentioned, apart from local measures, is the injection of trichophytin The value of this is still debated by strong protagonists and equally vigorous opponents. It is customary to administer the extract (1 100) intradermally with caution, beginning with 0 1 cc. Every three days the dose is increased by 0.1 cc unless the reaction is severe, in which case the next dose is omitted and future injections are begun at the next lowest dose. If trichophytin is administered, the dermatologist should watch carefully for flare of the primary eruption, since focal stimulation is not unknown

2. TOPICAL APPLICATIONS —Remedies for local use are listed in Chapters 2 and 25. The following situations present the commoner problems.

(*a*) *Maceration and fissures on interdigital webs and inner surfaces of toes (especially last two)* —In the absence of visible inflammation, it may suffice to apply a mild keratolytic preparation such as Whitfield's lotion each night for three or four nights, painting it on with a brush or cotton applicator. The resultant peeling may suffice to remove all the superficially invading fungi

ment of the patient and of contaminated areas in his environment was advised It has been shown by Broughton that in the British Army, relapse of tinea pedis could be attributed to infected shoes and socks. He advised use of nylon hose. If cotton or wool is worn, ordinary laundering may not destroy all spores. It is therefore desirable to immerse all socks in a 2 per cent cresol solution prior to laundering

The following simple rules are suggested as desirable for healthy feet and incidentally will help prevent infection with T. mentagrophytes

1. One should have a daily bath. The feet should be carefully dried, and purified talc or, better still, a talc containing 1 per cent thymol may be dusted liberally under and between the toes.

2 Loose and dead skin should be removed, and nails should be kept trimmed Callosities should be treated. Fungi grow in horny material

3. Attention should be given to flatfoot or other orthopedic conditions. These predispose to hyperhidrosis, which in turn favors invasion of a pathogenic fungus.

4. Hyperhidrosis may be relieved by soaking the feet for two to 10 minutes daily in a 25 per cent solution of Formalin Only sufficient solution is placed in a basin to cover the soles and reach part way up the sides of the feet. The solution is too strong for the dorsum of the foot. X-ray therapy is sometimes required.

5. Since autogenous infection resulting in nail disease is common, it may appear trite to warn against scratching an infected site.

6. One should avoid direct contact with infected animals. These may be domestic animals, such as the horse or cow, or laboratory animals, such as mice, as reported by Booth

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(*f*) *Onychomycosis.*—Nails infected by T. mentagrophytes usually show some inflammation at the base. Sometimes these nails are spontaneously shed. If only one fingernail is involved, surgical evulsion may be performed (for technique, *see* Chapter 25), or application of Whitfield's ointment to the base and under the nail may be advised. In the superficial variety (leukonychia trichophytica) scraping will remove the major portion of the disease. Application of Whitfield's ointment is usually effective for what remains.

(*g*) *Tinea capitis and tinea barbae.*—There is a tendency to self cure, with considerable inflammatory reaction. Hot wet packs should be employed, and hand epilation of all loose hairs in the area is useful. It is seldom necessary or advisable to resort to epilation with X rays or to inject foreign protein to induce fever

PROPHYLAXIS

There is considerable variation in susceptibility. Men are more vulnerable than women. This susceptibility is relative rather than absolute, as nearly every adult male has had at least the minor inconvenience of a fissure or some maceration on an interdigital toe web Because few civilians have severe and incapacitating infections, many persons believe that prophylaxis is unnecessary Some think also that attempts to prevent infection are futile and even unsound

We disagree with the latter concept, granting that it would appeal to lazy or indifferent persons

Just as a shampoo following a haircut is sound practice for children in the prophylaxis of tinea capitis, it is sagacious to wash the feet and apply 1 per cent tincture of iodine to the toe webs after use of a swimming pool, public beach, or Turkish bath In both cases, spores deposited on the skin may be removed or inactivated The regular daily use of a foot powder is a simple and yet effective preventative measure that is physiologically sound.

Persons with the active disease should exercise certain precautions to avoid contaminating other members of the family They should use paper slippers and never walk barefoot on floors, including that of the bathroom If the patient uses the tub or shower, it should be washed out with a 2 per cent solution of cresol The patient should have his own bath mat and towel

When apparent cure has been accomplished, the shoes and slippers may be sterilized by being placed for 24 hours in a shoe box in which a small open container holding 1 cc of 10 per cent solution of formaldehyde has been placed One should be careful that this liquid does not come in contact with leather The shoes should be aired for 24 hours before they are worn In a search for pathogenic fungi in shoes, Gillo and Getz were able to isolate T. mentagrophytes from 15 pairs of shoes out of 100 from which culture material was removed. This work was done in a prison, the incidence of tinea pedis among the prisoners was high. Simultaneous treat-

11. Trichophytosis

(Trichophyton rubrum)

TRICHOPHYTOSIS due to Trichophyton rubrum is a many-faceted disease entity characterized by a low grade inflammatory reaction and includes what is commonly known as chronic dermatophytosis and onychomycosis Follicular and other atypical infections are not uncommon; widespread eruptions are occasionally observed. Cure is characteristically difficult.

HISTORY

In the earlier literature on dermatophytosis (*see* Chapter 10), it was noted that T. rubrum was responsible for an appreciable percentage of cases. Hodge's report in 1921 focused attention on the disease as it affects nails. It was first reported by Lewis, Montgomery, and Hopper in 1938 that the cutaneous manifestations of T rubrum (T. purpureum) followed a pattern that was typical and constituted a disease entity Many case reports and articles have since enlarged the concept to its present important place in the dermatologic world.

ETIOLOGY

The causal agent, T rubrum, has many synonyms, including Trichophyton purpureum, Epidermophyton rubrum, Trichophyton rubidum, and Trichophyton plurizoniforme The distribution of the disease is world-wide, closely parallel to that of T. mentagrophytes There appears to be the same sex differentiation as well, with male patients far outnumbering female. The disease is commonly acquired early in life, although most patients are adults and many are elderly (particularly when toenails are the only site). King, Walton, and Livingood reported the case of a boy aged 12 months with tinea pedis due to T rubrum The disease is selective in that some persons appear to enjoy at least relative immunity. The manifestations

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A


C




D




B

may be aggravated by summer heat. Under tropical conditions, particularly when there is physical stress such as that experienced by members of the armed forces, the manifestations of the disease may increase in severity and extent. It is under such conditions, also, that the disease is more readily acquired. Rothman reported that of 20 patients with T. rubrum infections eight had increased tolerance (low or flat curve) when glucose was administered orally. Lewis, Hopper, and Scott observed three patients with widespread T. rubrum infections of the skin who had a coexistent lymphoblastoma (lymphatic leukemia, lymphosarcoma, and monocytic leukemia). The significance of these findings has yet to be assessed.

CLINICAL CHARACTERISTICS

1. DERMATOPHYTOSIS; TINEA CRURIS.—There is practically never vesiculation or acute reaction. The interdigital webs alone may harbor the organism, in which case the appearance does not differ noticeably from that of the latent form described in the section on Trichophytosis (T. mentagrophytes), although the duration is often considerably longer. Appearance of the eruption on the feet and on the hands seems to be peculiar to T. rubrum. Lesions of the feet may occur on the soles, the sides, the dorsa, the toes, or the nails. The plantar surface is a common site. When the hands are involved, the palms, the dorsa, the fingers, or the nails may be affected. Itching is frequent.

The entire sole is often involved, but the infection may be localized to a small area around the heel or on the ball of the foot. When the sole is involved, the infection usually extends to the sides of the foot and about the heel The infected skin is dull red and slightly thickened or indurated The scaling, which is constant, is usually fine and thin (branny), in contrast to the large flaky scale found in psoriasis or in some types of dermatophytosis The absence of visible vesiculation in the infected area is a persistent feature Hopkins and his group reported that in many of the patients with T rubrum infections studied at Fort Benning in 1942-1945, the eruption was acute, severe, and extensively vesicular This observation is at variance with the usual civilian experience and may be explained partially by the climate, the conditions under which the soldiers were living, and the probability that these young men were experiencing their initial attack There is usually a sharply marginated border along the outside of the foot, between the infected skin and the normal skin on the dorsum.

Small irregular infiltrated erythematous and scaly patches may be found on the dorsum of the foot and on the toes The degree of erythema may vary within a single patch There is no tendency to central clearing

The infection of the undersurface of the toes and of the interdigital webs is clinically similar to the infection of the sole, sometimes with the addition of a certain amount of maceration When the entire area about the toe is infected, the skin appears thickened and dry. Painful fissuring may occur about the joints

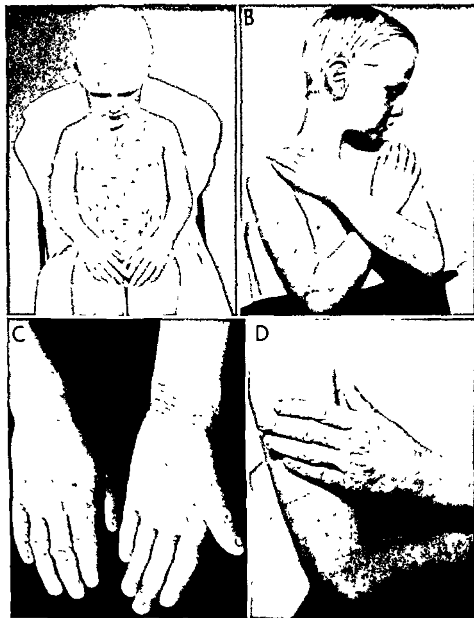


Fig. 50. Trichophytosis (T. rubrum) A, erythematous, circinate, and configurate lesions in orphan, aged 4, B, C, and D, same patient eight years later, with lesions widespread over body, including scalp, nails have not become involved

The eruption on the hands is similar to that on the feet. The entire palm may exhibit the characteristic dull red color, with thickening and scaling Friction and frequent washing in all probability make the scaling less apparent than that on the soles. The erythema may be slight and the condition thus be considered a callus. Isolated irregular patches may be present about the dorsum of the hand and on the fingers, as is the case with the feet. Frequently the skin of an entire finger is involved. Redness of the skin with or without scaling may be noted over the joints of the hands Fissuring in affected patches about the joints is a fairly constant feature. The absence of vesiculation except in rare instances and the presence of severe itching are again notable On several occasions when the palm was involved, we observed a marked decrease in the amount of sweat.

When the inguinal region or the upper inner thigh is affected, a dull red scaly plaquey eruption develops. The feet are almost always affected coincidentally, and often the disease is widespread. Itching is bothersome. In most cases the lesions are unilateral.

2 Glabrous skin lesions —It is on the nonhairy flat skin of the trunk and extremities that many different clinical expressions may be observed. These may be classified as follows

(*a*) *Scaly.*—A small area of ill-defined branny scaling with slight redness at the base may be the only manifestation of *T. schoenleini* or others of the endothrix Trichophyta, such as T. violaceum. T. rubrum also causes such a lesion, but usually more typical areas are also present. Microscopic and cultural studies are necessary for differential diagnosis.

(*b*) *Solid plaque.*—T rubrum is the cause of lesions which are not unlike certain lesions of psoriasis, being dull red and scaly on the surface, with slight thickening Bleeding points are usually not present when the scales are removed. The intensity of the color may vary in different portions of a single patch The shape of the lesions is not necessarily regular. The size of the patches varies from that of a pinhead to that of a half-dollar or larger. There is no tendency to central clearing. Lesions have been noted on various portions of the trunk, on the extremities, and, in a single instance, on the face At times the appearance may be urticarial or simulate erythema perstans, as reported by Waisman

(*c*) *Bizarre and configurate* —In this type, T. rubrum is the cause of an eruption which may involve large surfaces of skin on the trunk. The infection begins at one or more points and migrates in a thin line over an ever-widening area The affected skin is dull red and shows slight infiltration and scaling on the surface Behind the advancing border the skin is lighter than normal. *This suggests partial achromia Persistent itching is* a constant feature, and excoriations are usually seen

(*d*) *Tinea imbricata-like* —Kittredge described a widespread scaly eruption due to T rubrum The similarity to tinea imbricata was striking We have observed several similar cases.

(*e*) *Vesicular (dermatitis herpetiformis-like).*—In cases reported by

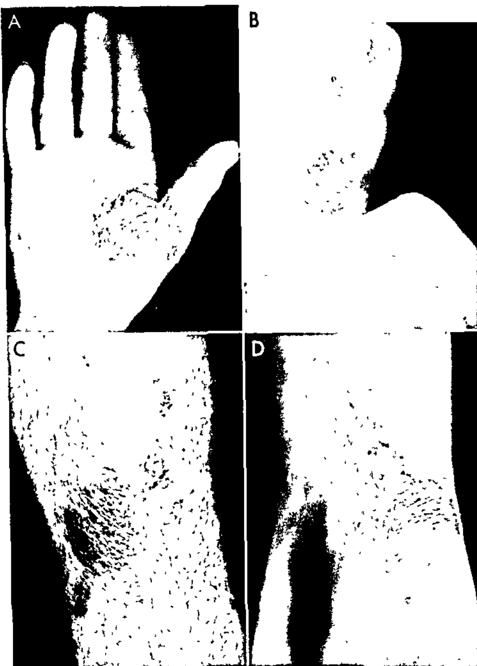


Fig 52 Trichophytosis (T. rubrum). Primary, subacute lesions In none of these four patients were other manifestations found in the more usual sites **A,** erythematous and scaly area on boy **B,** bullous lesion **C,** multiple edematous lesions on leg **D,** recent, gyrate, scaly, eczematous-like plaque

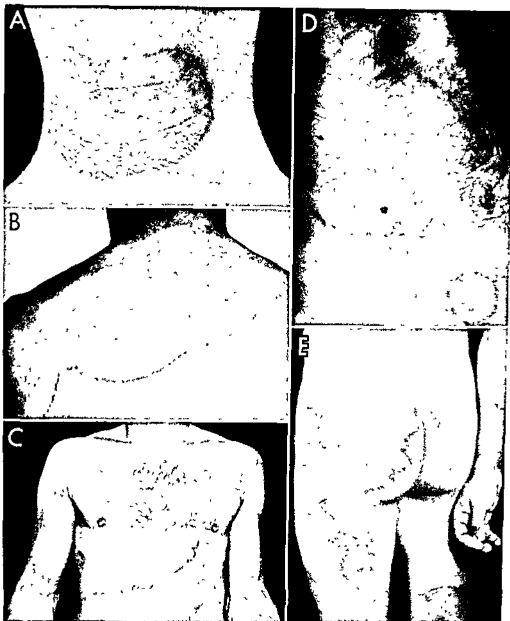


Fig 51 Trichophytosis (T rubrum) A, thickened, dry, scaly plaque on back of neck B, extensive involvement of upper back, active border is elevated C, similar widespread rash over trunk and shoulder girdle D, annular and gyrate lesions E, plaquey, pruritic, dull-red, and scaly lesions with nail involvement

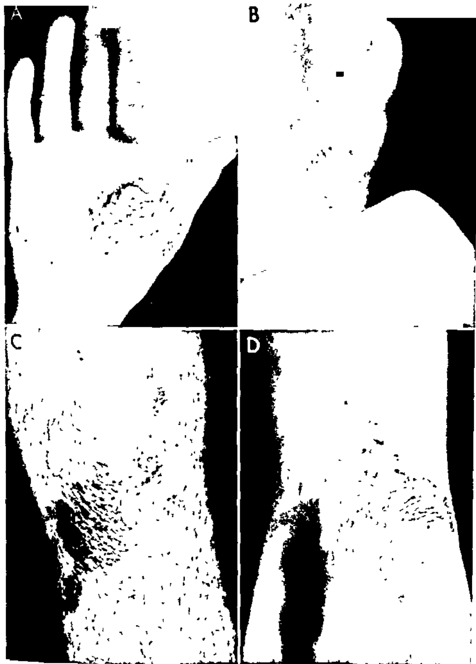


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Costello, Tolmach and Schweig, and others, a widespread vesicular and vesiculobullous eruption, having features of Duhring's disease (particularly grouping and symmetric distribution), yielded T. rubrum after mycologic study. There were usually serpiginous borders and coalescence of lesions. It is possible also that the mycotic findings may reveal a superimposed fungous infection in patients with dermatitis herpetiformis.

3. Involvement of nails.—Nails infected with any pathogenic fungus except C. albicans are usually opaque, lusterless, friable, and yellowish. Varying degrees of dystrophy, as evidenced by irregularities of the nail plate, separation of the nail, and subungual hyperkeratosis, are infrequently present.

Nails infected with T. rubrum sometimes have certain features peculiar to this organism Unlike ungual infections caused by T. mentagrophytes, the condition due to T rubrum does not often concomitantly involve the interdigital webs of the toes Furthermore, a superficial location of the infection on the surface of the nail is frequent with T. mentagrophytes but practically unknown with T. rubrum The duration of the infection is shorter and the progress of the infection is faster with T mentagrophytes

The onset and progress of ungual infection due to T. rubrum is slow and insidious. When the condition is first observed, one or more nails may be involved The patient, who has applied for treatment of infected fingernails, may unknowingly have involvement of the toenails and even of the feet. There is little reaction in the subungual and paronychial tissues. We have not observed paronychia in our cases (Compare infections due to T. mentagrophytes or to C albicans)

The infection usually begins under the free border or along the lateral margins of the nail plate. We have observed an occasional case in which the infection started in the proximal portion of the nail Yellow or white vertical streaks may appear in the nail, seeming to result from separation of the nail plate from its bed. These streaks gradually widen, the nail separates more and more and debris accumulates. There may be gradual involvement of the distal end of the nail without the usual formation of streaks Meanwhile the nail itself becomes thinned, owing to gradual invasion of the fungus The nail becomes brittle, and the distal portion may be broken or worn off, leaving only the proximal part Sometimes the entire nail plate is lost, leaving the nail bed covered with scales and debris

We have been able to isolate T rubrum only once from the surface of a nail obviously infected by fungi and never from a nail with no clinical evidence of fungus involvement. In connection with these observations, we wish to point out that scrapings from the surface of an infected nail frequently contained the ordinary saprophytes but when scrapings from the deeper portions of the nail were planted on agar slants, T. rubrum in pure culture resulted For this reason cultures of infected nails should be taken from different depths in the nail substance Unless the deeper portions are

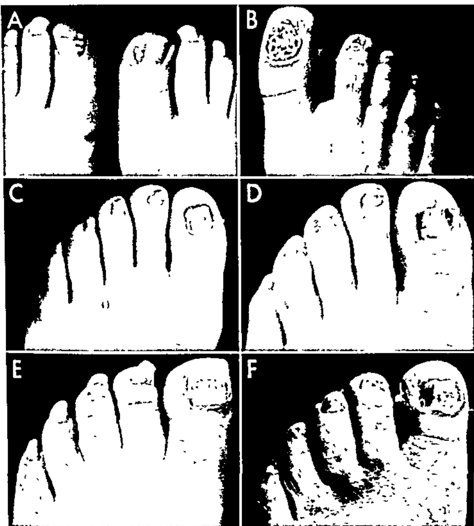


Fig. 53. Trichophytosis (T. rubrum) Invasion of toenails results in friability, opaque-

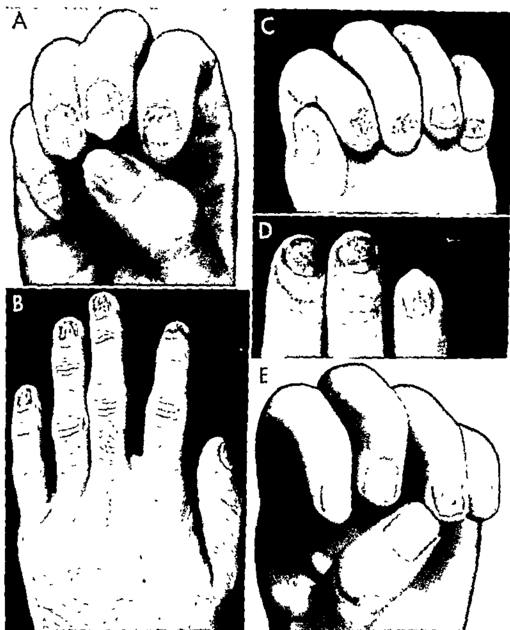


Fig 54. Trichophytosis (T rubrum) A, [illegible] last four digits B, involvement of all [illegible] discoloration and dystrophy C, thumb [illegible] who received only sporadic treatment D [illegible] E, nails of thumb and ring finger chalky white and thickened



patient with lymphoblastoma

on the possibility of other significant lesions The work of Thompson, White, and Naide implicates T. rubrum as a cause of thromboangiitis obliterans, thrombophlebitis, and other diseases of blood vessels, but confirmation is lacking. That T. rubrum was the cause of the clinical manifestations in the case reported as eosinophilic granuloma by Lewis and Cormia is an intriguing possibility but not proved.

DIFFERENTIAL DIAGNOSIS

As in the diagnosis of other forms of mycotic infection, laboratory methods should be employed for every patient suspected of having this fungous disease. The information to be obtained by such studies is frequently the only means of definitely establishing the diagnosis.

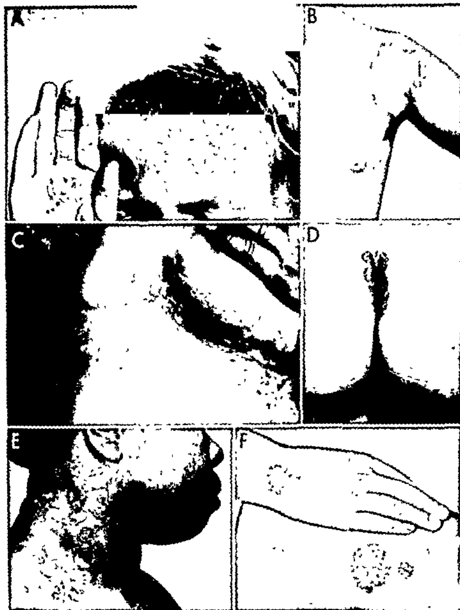
1. GLABROUS SKIN (INCLUDING DERMATOPHYTOSIS).—(*a*) *Other fungous diseases.*—The disorder caused by T. mentagrophytes may be indistinguishable if the lesions are confined to the toe webs. As a rule the latter disease is evidenced by vesiculation and a more acute inflammatory reaction. When the inguinal region and the upper thigh are affected, the resemblance to epidermophytosis may be close. Often, in the T. rubrum infection the disease is unilateral, whereas the E. floccosum disorder is characteristically bilateral.

(*b*) *Psoriasis* —So-called aberrant types of psoriasis are often due to T. rubrum. While the diagnosis can be made with certainty only from mycologic examination (usually repeated several times), lack of involvement of the scalp and localization to areas not commonly the sites of psoriasis, such as the palms, the soles, or the inner surfaces of the thighs, should make one suspicious The presence of bleeding points after removal of the scale is not usual with the mycotic disorder. The histologic picture usually observed with psoriasis is absent in fungous infection Pruritus, if severe, favors the diagnosis of dermatophytosis

(*c*) *Neurodermatitis (atopic eczema)* —On close inspection, the affected patch will be seen to be lichenified, with exaggerated cutaneous markings Scratch marks may be noted, as with the fungous disease. Careful investigation of the history will elicit the fact that pruritus and scratching by the patient preceded the rash There may be a history of allergy to foods or to inhalants or a tendency to another allergic disorder, such as hay fever or asthma

2. NAILS —(*a*) *Infection with C albicans* —Chronic paronychia is practically constant The edges of the nail become yellow and eroded or develop a dark stripe, but the nail substance is frequently firm and translucent Uneven ridges and grooves are probably due to interference with nutrition Most of these signs are not seen in nails infected with T mentagrophytes or T rubrum

(*b*) *Psoriasis* —Pitting of the nails is frequent. Ridges and grooves



F, pyoderma

sometimes develop. Rarely, a lesion of psoriasis develops in the nail bed. In this case the lesion is well demarcated, and there may be redness, which fades on pressure over the nail. The color of psoriatic nails usually remains unaltered, although a yellow tinge may appear. The nail tends to remain firm and translucent.

(c) *Pyogenic involvement of paronychial tissues.*—This produces an acute, painful, bright-red swelling. There may be a hangnail or some evidence of injury. The disease is of a few days' duration. Dystrophy of the nail, as evidenced by ridges and grooves, may result from interference with nutrition.

(d) *Syphilis.*—This disease may affect the nail or the paronychial tissues. A chancre may appear, and considerable destruction of tissue with painful swelling of the parts is common. Another form of syphilitic involvement of the ungual tissues, usually seen in association with a late cutaneous or other manifestation, results in atrophy of the nail.

(e) *Other diseases.*—Tuberculosis and leprosy also affect nails and the surrounding tissues, dystrophies of various degrees being present

(f) *Other fungous infections.*—In the clinical diagnosis of fungous infection of the nails, one should remember that chronic paronychia with secondary changes in the substance of the nail is usually due to C. albicans. In the invasive type of filamentous infection, the cardinal symptoms of yellowness, friability, and opacity of the nail and the negative sign of lack of paronychia usually point to the correct diagnosis The white specks or patches frequently seen on the edges of toenails are due to the presence of T. mentagrophytes.

3. FOLLICULAR INFECTION —*When the scalp is involved, a type of* fungous infection will probably be considered. Since adults may be affected, other scalp disorders, such as pyogenic folliculitis and seborrheic dermatitis, may cause some confusion. Presence of foci of the typical chronic disease on the feet, hands, or nails should increase one's awareness of the possibility of a scalp or beard hair follicle infection due to T. rubrum.

4 GRANULOMATOUS INFILTRATIONS —In the not unusual granulomatous lesions of the leg, the patient has a coexisting infection of the glabrous skin of the feet and often of the toenails It is usually unilateral. Erythema induratum produces ulcerating lesions, larger than the fungus granuloma Pyoderma, drug eruption (particularly due to a halogen), pernio, and erythema nodosum may give difficulty in an occasional instance but may be readily differentiated if cultures and biopsy are done

PATHOLOGY

1 *GLABROUS SKIN LESIONS —There is a simple inflammatory process* in the upper part of the cutis The vessels are slightly dilated, cellular elements are of the small round type and are sparse. There is moderate inter-

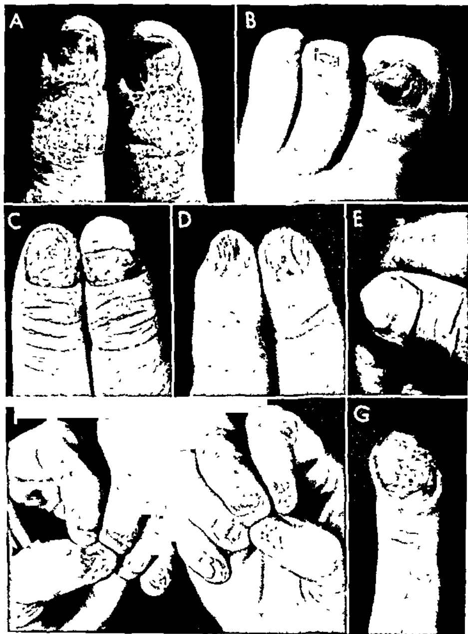


FIG 58 Nonmycotic disorders simulating onychomycosis A, psoriasis [illegible]

stitial edema. The epidermis is slightly acanthotic. At times there is marked hyperkeratosis. The basal cell margin is intact. There is no intercellular edema, spongiosis, or vesicle formation, occasional areas of parakeratosis are noted.

2. Granulomatous folliculitis —This has been described as follows:

(*a*) *Satenstein (case of Harris and Lewis).*—Under low power magnification, there is an intense cellular infiltration, somewhat focal in the upper cutis and more diffuse in the mid and deep cutis, extending down into the fat. This infiltration is more pronounced around the vessels and hair follicles. The blood vessels and lymphatics in the upper cutis are dilated. There is an interstitial edema of the collagen in the upper cutis and a parenchymatous edema in the mid and deep cutis. Muscle fibers present are in a state of hyaline degeneration High power magnification shows the infiltration in the upper cutis to be predominantly lymphocytic. In the mid and deep cutis it is a mixture of lymphocytes, connective tissue, and plasma cells. Mast cells are present in large numbers The percentage of polymorphonuclear cells is highest near the hair follicle. The vessel walls of the upper cutis are edematous and the nuclei of the endothelium project into the lumen. The connective tissue in this zone is for the most part dissociated and granular. Granulation tissue is present in the mid and deep cutis The walls of the vessels in the deep cutis are markedly swollen and in places show hyaline degeneration. The nerve bundles are swollen and degenerated.

(*b*) *Wilson, Plunkett, and Gregersen.*—There is a mass of infiltrate around an infected hair situated within a follicle whose wall has undergone more or less necrotic destruction. The infiltrate is polymorphous and is composed of epithelioid cells, fibroblasts, giant cells, plasma cells, and lymphocytes. The reaction is predominantly chronic but some areas show acute microabscesses crowded with polymorphonuclear leukocytes and numerous eosinophils Various degrees of cicatricial healing have been observed With the Hotchkiss-McManus stain, spores in chains or in mosaic masses are readily demonstrated, often deep in the cutis, but always in the presence of necrotic material

MYCOLOGY

1. Direct examination —Relatively few fungus filaments are noted. Repeated tests may be needed to demonstrate the presence of fungus When the hair follicle is invaded the fungus is seen to be an ectothrix Trichophyton

2 Cultural characteristics —In the primary growth, the culture at first is fluffy, pure white and hemispheric. Later the edge of the colony is less fluffy, becoming almost velvety Sometimes the central umbo is lacking Radial grooves may appear The back of the colony soon develops a

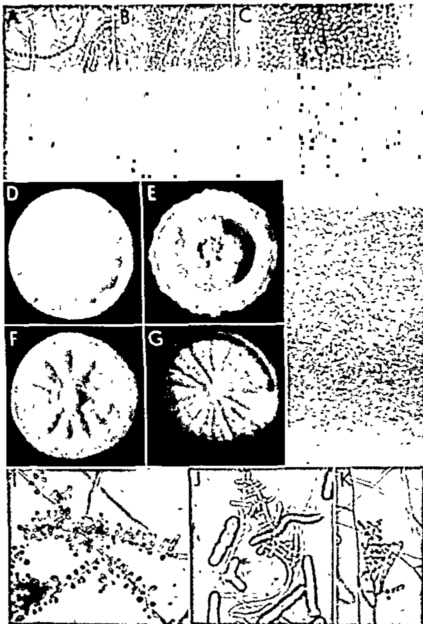


Fig 59. T
nail scraping
hair, showin,
colony form
tiple radial f
lacey, and c
revealing microconidia and fuseaux, × 430

typical rose-purple color. This gradually spreads to the edge of the older colony and may later be noted in varying degree throughout the colony.

If the aerial growth is abundant, the colony appears white and fluffy *and the rose-purple color can be seen only from the back. When the growth* is sparser, the color may be seen from the top. This fact accounts for many of the variations in the color of the colony. The appearance of colonies with a minimal aerial growth varies from powdery to granular.

3. CULTURE MOUNT.—Vegetative filaments are simple and show little variation. The microconidia are produced *en grappes* or along the mycelium as sporiferous hyphae. In fluffy colonies microconidia predominate. There is little evidence of fuseaux (except when they are searched for). In granular colonies abundant fuseaux may be seen and microconidia are scant *Racquet mycelium and chlamydospores will be observed if the nutrition of* the medium is reduced.

4. BIOPSY OF CULTURE.—In young specimens the fringe is distinct and filamentous, in older specimens it is mostly wide and lacy. On high power magnification a moderate number of microspores are to be seen. Part of a fuseau may be observed. The core is dense and deeply pigmented; it is sharply demarcated above and below and consists of tightly packed hyphae and some chlamydospores There is invasion of the substrate by small-calibered mycelium, usually sparse in amount and poorly stained.

5 FILTERED ULTRAVIOLET RAYS —Without experience one has difficulty in distinguishing between T. mentagrophytes and T. rubrum. In an early colony of T. rubrum the color is a bright, light blue, which is present throughout the colony or, if the colony is very fluffy, at the periphery alone. In older colonies a light-blue border is characteristic.

6. ANIMAL INOCULATION.—This is occasionally successful. Reiss found that rabbits which had been castrated or had received X-ray exposures to the abdomen could be infected at will.

7. DIFFERENTIAL DIAGNOSIS (LABORATORY).—The main species of fungus to be differentiated is T. mentagrophytes. The cultural growth of T. rubrum is typical when starting and developing, and the tinctorial changes are characteristic. (*See* also the preceding chapter on T mentagrophytes) *In culture biopsy, the appearance is often similar to that of* T mentagrophytes, but the ratio of spores to hyphae is much less and there is less tendency to clusters; lack of spirals and nodular organs is confirmatory.

IMMUNOLOGY

The delayed tuberculin-type reaction to trichophytin is slight or absent in patients with this infection The more usual response is an immediate wheal reaction with pseudopods (*see* Chapter 24, the section on "Trichophytin").

PROGNOSIS

Since T. rubrum approaches the position of living in a state of equilibrium with the host, with often only a token of inflammatory reaction, this disease is to be included with the least satisfactory mycoses so far as curability with complete eradication is concerned. The longer the duration, the more difficult it is to obtain good results. Lesions on the palms and soles and nail involvement are usually less responsive to treatment than plaques in less hyperkeratotic flat areas of skin. In the rare instances in which *the patient has shown the delayed tuberculin type of reaction to the* intradermal trichophytin test, there has been a satisfactory response to treatment. A great deal depends on the attitude of the patient. If he is easily discouraged, treatment will probably fail. If he is determined and co-operates fully, there is much more hope.

TREATMENT

1. Skin (dermatophytosis, tinea cruris, infection of glabrous skin).—Our methods and their results leave much to be desired. At the outset it is best to spend some time with the patient, explaining the nature of the disease and the fact that patience and active co-operation are of the essence It is a temptation to assume a defeatist attitude. However, it is usually possible to achieve cure, and it is justifiable to encourage a patient to spend the requisite time and to go through the necessary inconveniences.

Except for the nail disease, chief reliance should be placed on remedies applied directly to the infected tissue These may be selected from those listed in Chapter 25 There is rarely any danger of a focal flare in the diseased skin, but one should guard against primary irritation in patients with undue sensitivity or with lesions on or near the face, on the genitalia, or on the dorsa of the feet and hands Care in regard to the strength of an ointment to be applied is important also when the lesions involve large areas of skin

In the localized form on the soles, it is customary to begin with Whitfield ointment at one-half strength, with instructions to rub it in well once or, better still, twice daily If no irritation develops in one week, the strength should be doubled Thereafter the procedure varies with the patient It is unwise to change formulas too frequently, but if after two or three weeks the response is poor, it is often advantageous to utilize another remedy. There is no good evidence that any of the remedies listed are specific, but better results are obtained when the attack is varied from time to time. It should be understood that rubbing ointment on the skin becomes a tedious business and some variety is, for the patient, a partial relief from this monotonous and disagreeable routine.

When the more delicate sites are involved, the routine may vary some-

what. For instance, if a plaque is present on the upper inner thigh, an ointment containing salicylic acid and sulfur precipitate (*see* p 239) is usually well tolerated and does not cause edema or contact dermatitis of the genitalia. When stronger remedies are used by a male patient it is often helpful for him to wear a suspensory to guard against direct contact. In this connection, one must be careful not to overlook involvement of the scrotum.

It is not always easy to know when the patient has achieved cure. If evidence of the disease is lacking, one is still well advised to continue treatment for several weeks. Arbitrarily, therapy is then abandoned, to be followed in a week or two by observation and cultural studies. It is not unusual for the disease to recur after apparent cure. Recurrence, of course, means that therapy must be immediately resumed.

The subject of prophylaxis is much debated. The measures outlined for trichophytosis (T. mentagrophytes) in Chapter 10 apply also to this disease. It is unwise to depend on what others may or may not do in regard to personal hygiene or therapy of a mycosis. Public health measures are either lacking or are relatively ineffective.

Other available procedures, such as fractional X-ray exposures or treatment with ultraviolet radiation, are no help with this disorder. Attempts at cure by means of trichophytin injections have been futile, and this treatment is not indicated. We also advise against the potentially hazardous camphor-phenol applications which achieved favorable but undeserved notoriety through publication of an article in a lay journal. We are still hoping for a satisfactory antibiotic drug.

2 Nails —In the rare instance in which the disease has been acquired in a fingernail, probably during a manicure, and has remained in this site, the best therapy is surgical evulsion, the technic of which is outlined in Chapter 25 This treatment provides rapid and fairly certain cure and eliminates the threat of spread. When more than one nail becomes involved and involvement becomes more serious with each additional nail, surgical evulsion must be considered an available but not necessarily an indicated remedy Recurrences are commoner when several nails are affected, particularly when the disease has also invaded skin Results are poor when several infected toenails are surgically evulsed, even when the disease in other parts of the feet appears under control In cases of extensive involvement, surgical evulsion may nevertheless be utilized as part of an over-all attack on reservoirs of infection after other sites have been treated conscientiously for several months It is often a serious handicap to have diseased fingernails The handicap may be of cosmetic (esthetic) nature, as in the case of a sensitive person with intimate contact in a business or profession with other (perhaps critical) people. Or the diseased nails may be a menace, as when the patient is a nurse, physician, barber, manicurist, or personal maid, having intimate contact with other human beings in the course of work The danger of person-to-person transfer of fungous spores is not usually considered to be too great in casual contacts,

such as shaking hands, or through the medium of a common object, such as the subway strap, although the true importance of such transfer has not been determined. In any case, infected nails and lesions on the palms are foci of potential importance.

As an alternative to complete surgical evulsion, a more conservative routine would include some form of abrasion or partial nail removal. If care is used, a great deal of diseased nail can be cut away with a sharp scalpel Nail that has separated from the base may be clipped away with a nail clipper. An emery board, sandpaper, or an abrasive steel brush on a rotary device similar to a dental drill are all means of removing diseased nail. All the material so removed should be collected and burned. It is customary to plan disposal ahead of time by covering the nearby floor with newspaper. Partial evulsion should be repeated frequently and regularly. Local applications to the remainder of the nail and to the base include those described in Chapter 25. None of these remedies, including the combination of drugs advocated by Rothman, shows any specific effect, but often such a scheme is useful to dramatize the treatment in the mind of the patient. If an ointment such as Whitfield's is applied, some form of covering is usually desirable to keep the medicament from being rubbed off and the effect dissipated Cotton gloves have the disadvantage of carrying the grease from the nail to skin areas. This not only works to the disadvantage of the nail but may irritate the skin. It is often possible to achieve optimum results by covering the nails with adhesive and leaving it on overnight. If several nails are involved, this procedure adds considerably to the time required for application However, it seems to add to the effectiveness, perhaps encouraging some deeper penetration of the drugs. One must be careful that seepage of the drugs under the adhesive does not overly irritate the surrounding skin.

3. Folliculitis —For follicular lesions, manual epilation of infected hair repeated usually at intervals of one week is important Removal of the stubs is not always readily accomplished, but there is no adequate substitute. Roentgen epilation is rarely indicated and should be reserved for patients with strictly localized lesions, usually when hand epilation has been a failure. In addition to epilation, some form of local remedy within the tolerance of the patient and the particular area involved should be prescribed

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12. Epidermophytosis
(Tinea cruris)

EPIDERMOPHYTOSIS (tinea cruris) is a superficial fungous infection usually confined to the inner surface of the upper parts of the thighs. There may be contiguous spreading, or other parts of the skin may become affected In India the disease is known as dhobie itch. It is sometimes still referred to as eczema marginatum, under which term it was first described by Hebra in 1860.

ETIOLOGY

The disease is caused by Epidermophyton floccosum. It may be spread by infected articles of clothing or by an athletic suspensory, but at times the exact method of dissemination is unknown. It has been shown by Sanderson and Slope that the feet are a not uncommon source of dissemination of the fungus to the groin and elsewhere. There have been epidemics, such as that reported by Mercer and Farber. The localization is in part explained by the affinity of the fungus for intertriginous areas. The crural region may also be the site of mycotic infections due to C. albicans, T. mentagrophytes, and T. rubrum

CLINICAL CHARACTERISTICS

The rash on the upper inner thighs is well marginated, the surface is scaly, and the border shows minute vesicopustules. There is little or no tendency to central clearing The lesions are brownish, with some redness due to inflammation. The eruption is usually bilateral and symmetric, it favors the upper inner portions of the thighs but may extend up to the pubis and as far back as the sacrum The genitalia may share the infec-

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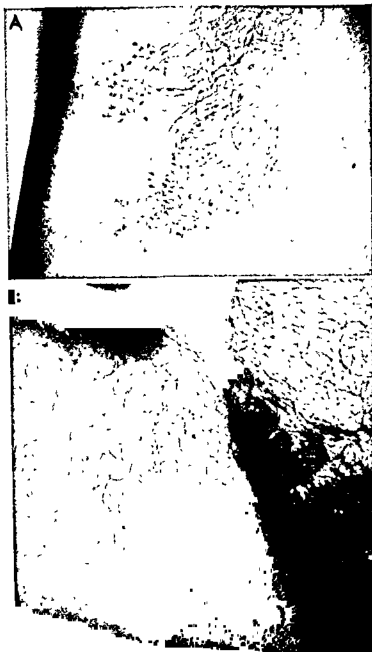


Fig 61. Epidermophytosis (E floccosum). A, plaquey involvement of axilla B, well demarcated, subacutely inflamed area on upper inner thigh without any tendency to central clearing



Fig 60. *Tinea cruris.* Bilateral rash with well-defined elevated edge and scaly surface is characteristic Culture yielded E floccosum

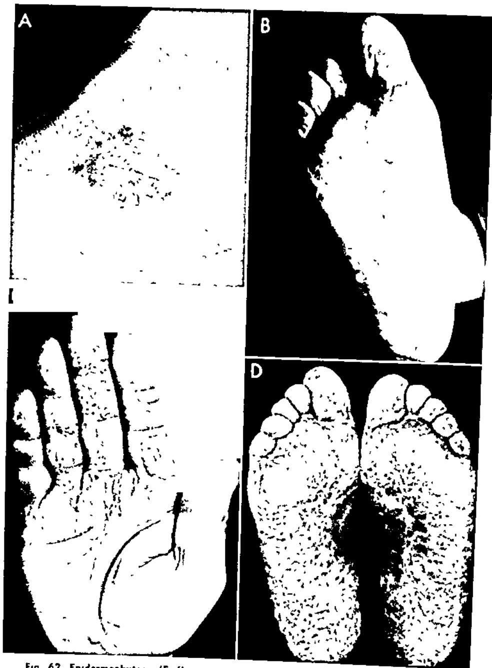


Fig 62 Epidermophytosis (E floccosum). A, superficial, circinate, vesicular patch on dorsum of foot B, superficial, scaly and erythematous eruption on sides of toes and on sole C, erythematous, scaly, and occasionally vesicular eruption D, profusely scaly, moderately thickened, and mildly erythematous eruption over plantar surfaces

fection. Vesicopustules are sometimes seen on the soles In all cases the feet should be examined, since the lesions there may be minimal and asymptomatic. With the friction of clothing, especially during the heat of summer, varying degrees of secondary eczematization occur. Follicular involvement is unknown. We have never found E floccosum in nail tissue

DIFFERENTIAL DIAGNOSIS

In cases of infection with T. mentagrophytes, the feet usually have previously been involved and inflammation is more marked, as evidenced by vesiculation and exudative patches. Localization to the intertriginous parts is more pronounced. With infections due to T. rubrum, dull-red, scaly, thickened plaques may be found in the crural region as part of a widespread eruption, itching is more marked than when the infection is due to E floccosum or to T. mentagrophytes and the distribution is usually unilateral, in contradistinction to the type caused by E. floccosum.

There may be some confusion with erythrasma and moniliasis, particularly when areas other than the groins are affected. The red border of the former disorder and the moist character of the latter are distinguishing features. Psoriasis and seborrheic eczema may also be simulated, but these diseases are rarely confined to this location.

MYCOLOGY

1 Direct examination.—Chains of spores in which the elements tend to be flattened are frequently noted in fairly large numbers. When the scaling is profuse, large amounts of fungous material will be observed.

2 Cultural characteristics —Growth begins slowly and may not be apparent for two or three weeks. It then continues at a moderate rate. The colony has a velvety or felted surface with irregular folds and grooves; the surface may be smooth The aerial hyphae are few The color is characteristically grayish olive-drab but sometimes is greenish drab. Pleomorphic growth, as evidenced by whitish tufts, is common, appears early, and may eventually cover the entire agar slant

3 Culture mount —Club-shaped fuseaux with blunt ends in groups resembling bunches of bananas are frequently found in specimens from the growth with a fluffy surface Chlamydospores are abundant in the subsurface part of the colony. Racquet mycelium is often seen, but other vegetative and reproductive forms are infrequent. Tightly coiled spirals are observed with some strains on corn meal agar

4. Biopsy of culture —The specimen is grossly wavy or undulating The fringe is lacey and narrow. in it are blunt-end fuseaux in small numbers as well as segments of the same The core is moderately dark and distinctly cellular Under higher magnification, these chlamydospores are noted to be variously-sized, are mostly large, and are often irregular in

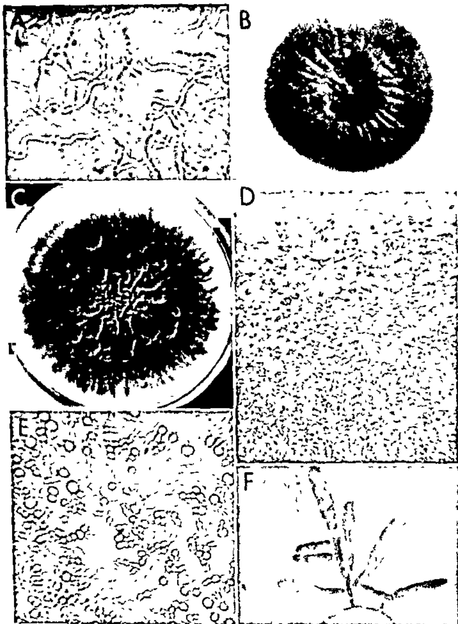


Fig 63 Epidermophyton floccosum A, numerous wavy filaments present in direct mount from scales × 400 B, colony after three weeks [illegible]
with radial [illegible]
tufts **D,** sec [illegible]
ture mount [illegible]
revealing group of macroconidia, × 500

shape. They are present in the background of amorphous material. Very few hyphae are noted The immediate substrate shows lighter-staining hyphae. There is gradual reduction in the number of hyphae, with virtually none in the lower substrate.

5. FILTERED ULTRAVIOLET RAYS.—In about two weeks the colony is clear, dull, and dark olive.

6. ANIMAL INOCULATION.—Animal inoculation is not successful.

7. DIFFERENTIAL DIAGNOSIS —In a direct mount, if the filaments are numerous, infection with E. floccosum may be surmised The cultural growth can hardly be confused. The finding of clusters of fuseaux with blunt ends in a culture mount is characteristic In culture biopsy, blunt-end fuseaux in the fringe and a distinctly cellular core (mostly chlamydospores) are typical. Similar large cells are seen in the core in both T. schoenleini and T. megnini cultures, but these will be observed to be giant-sized filaments.

IMMUNOLOGY

E floccosum usually does not initiate sensitization to trichophytin. A test with trichophytin as a rule elicits a negative or a mildly positive reaction

PROGNOSIS

The ordinary form of the disease tends to respond readily to medicinal applications. Relapse is common, it is probably due to ill-timed stopping of the treatment or to reinfection from untreated parts or from clothing

TREATMENT

Against the ordinary form of the disease, one of the following topical applications may be used.

1 Salicylic acid 3 per cent and precipitated sulfur 6 per cent in equal parts of lanolin (hydrous wool fat) and petrolatum It is advisable to begin with this concentration, but if on the next visit there is no evidence of irritation, the strength of both drugs may be doubled With nightly applications of this ointment the patient is usually cured in three weeks or less.

2 Resorcinol 3 to 12 per cent in lotion of zinc oxide; advocated by Wise The peeling effect of the resorcinol is tolerated better in this medium than in a grease

3 Compound ointment of benzoic acid (Whitfield's ointment) with 3 per cent salicylic acid and 6 per cent benzoic acid If there is no cutaneous reaction, the strength of the ingredients may be cautiously increased

It is inadvisable to use chrysarobin or thymol unless previous medication is unavailing. When there is a marked inflammatory reaction, soothing

13. Candidiasis

(Moniliasis)

CANDIDIASIS is a syndrome embracing a number of manifestations which until this era were considered to be unrelated. Although the skin is the commonest site, the infection may invade the lungs and, rarely, other organs. The causative fungus is a yeastlike organism, *Candida albicans*

HISTORY

In 1839 Langenbeck demonstrated fungi in material taken from a patient with thrush Robin published a description of the microorganism in 1843 and named it *Oidium albicans*. The various manifestations of the disease were recognized and studied by many different investigators, and an involved nomenclature came into use. Through the work of Kaufman-Wolf, Fabry, Kumer, Ravaut, Hopkins, Benham, and others, the relationships of the various rashes and conditions have come to be better understood Schamberg, in 1915, was one of the first in the United States to report a case of generalized cutaneous thrush Engman in 1920 described a case of moniliasis localized to the upper parts of the thighs, the vulva, and the inframammary regions The article by Shelmire and that by Beeson and Church were also early contributions

ETIOLOGY

The causative microorganism, *C albicans*, is seldom if ever found on normal skin Other yeastlike fungi should not be confused with it The organism is a common inhabitant of the gastrointestinal tract, where it seldom causes any symptoms Through the investigations of Ashford and others, it was considered to be of etiologic significance in sprue, but later research does not appear to bear out such a relationship

The incidence of the localized types of infection increases with age.

applications should first be applied. A 1 per cent aqueous solution of gentian violet (methylrosaniline chloride) may be painted on the affected skin. If the infection is still present after the inflammatory reaction has subsided, one of the aforementioned prescriptions may be used. The only indication for the use of roentgen rays is a secondary or associated eczematous eruption. Ultraviolet radiation is not helpful.

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The causative microorganism, *C albicans*, is seldom if ever found on normal skin Other yeastlike fungi should not be confused with it The organism is a common inhabitant of the gastrointestinal tract, where it seldom causes any symptoms Through the investigations of Ashford and others, it was considered to be of etiologic significance in sprue, but later research does not appear to bear out such a relationship

The incidence of the localized types of infection increases with age

There is a more or less corresponding increase with age in the presence of the fungus in the gastrointestinal tract. Relapse of cutaneous lesions may take place when a systemic or debilitating illness is experienced. The resistance of the patient to C. albicans is decreased by diabetes, probably because the storing of sugar favors the growth of the organism. We have noted that a large percentage of patients with some form of cutaneous moniliasis are obese. The organism is more apt to find suitable soil in persons whose skin is macerated by frequent or prolonged immersion in water. Housewives, bartenders, waiters, and bakers appear to be more prone to the condition because of their occupations. Profuse sweating may be followed by moniliasis. The organism is probably of weak pathogenicity, but once the disease state is established, the condition is apt to persist indefinitely. The organism multiplies rapidly, it may be isolated from such diseased tissues as those of carcinoma, and it may be found in the sputum of a patient approaching death. In such instances, one must be careful to differentiate between the saprophytic and the pathogenic significance It is probable that the virulence of C. albicans may so increase that the fungus is capable of causing an infection without any apparent predisposing factor. The series of cases of perlèche of children in an orphanage, as reported by Finnerud, *may be cited as a possible example The mother of a baby* exhibiting thrush frequently has one of the intertriginous forms or a vaginal moniliasis Genital moniliasis affecting husband and wife was studied by Waisman and found to be more frequent than before antibiotics were so commonly prescribed. An almost complete lack of resistance to the fungus explains the rare instances of granulomatous lesions in children and the even more uncommon cases in adults The broad-spectrum antibiotics have come under suspicion as important agents in lowering resistance to C. albicans In particular, the development of intertrigo involving the perianal tissues and pruritus with maceration in this area has been considered a direct effect of the administration of these drugs by mouth. Such an effect has been noted often in patients in whom diarrhea has developed after antibiotic therapy Speculation as to the reason for this skin effect includes the explanation that competing microorganisms are destroyed, but a direct growth-stimulating effect on Candida has also been thought possible (Woods, Manning and Patterson, Johnson) Kligman, Robinson, and others doubt the role of the antibiotics as a factor in the development of candidiasis It would seem that the chief danger of serious and perhaps systemic infection with Candida is in elderly patients who receive a prolonged course *of an antibiotic drug In younger persons, particularly when* the drug is given for only a short period, any untoward effect of the antibiotic is soon overcome

CLINICAL CHARACTERISTICS

The intestinal tract of a patient with cutaneous moniliasis, as well as that of a person with no cutaneous manifestations, frequently harbors C.



[illegible]

of toe web

albicans. The percentage of persons with stool cultures yielding C. albicans increases with age (Lewis and Hopper).

The manifestations of C. albicans may be grouped as (a) localized, (b) of moniliid type, (c) generalized cutaneous and granulomatous, and (d) systemic.

1. LOCALIZED FORMS.—(a) *Onychia and paronychia.*—It is chiefly the fingers which are affected, although we have observed instances of infection of the toenails. There may be involvement of only one digit, but multiple infections are not infrequently seen. The paronychial tissues are usually the first to be involved, and the condition may appear not unlike a pyogenic infection. There is usually little or no pain except on pressure, but sometimes the parts throb. No pus will be found if the tissues are incised; a thin purulent discharge may appear under the nail fold. The lateral margins of the nail often reveal a narrow dark-green striping. Transverse ridges may develop The nail remains hard but gradually becomes thickened and distorted, particularly at the edges. The color may not change, or it may become brownish. Usually the shine is unaffected The proximal portions or the edges of the nail sometimes become eroded. It is at once apparent that the cardinal signs of tinea unguium due to T. rubrum, namely, crumbling, yellow color, and loss of luster, together with lack of paronychia, readily distinguish the two conditions.

(b) *Intertrigo.*—Well-defined, bright-red, exuding patches with scalloped borders give a fairly characteristic picture of monilial intertrigo Outside the zone of intertrigo, small flaccid vesicopustules may be noted. There is usually a bright-red border of skin around the satellite lesions According to Hopkins, these represent the primary lesions from which intertrigos develop The common sites of monilial intertrigo are the axillae, the inframammary folds, the groins, the umbilicus, the interdigital webs of the feet, and the intergluteal fold. The process may extend from a primarily intertriginous location to the flat skin, and large sheets of skin of a susceptible person may be affected It may be pointed out that interdigital involvement of the toes may be mistaken for dermatophytosis caused by filamentous fungi. Usually if C albicans is the cause, all the webs of the toes are involved. A bright-red color and soreness, with satellite vesicopustules, also favor a diagnosis of moniliasis Similar lesions on the hands and at the angles of the mouth have distinct names

(c) *Erosio interdigitalis blastomycetica* —This form of intertrigo affects the interdigital webs of the hands (usually the third or fourth) The lesion has a bright-red base with a moist surface and peeling border The lesions are tender rather than pruritic

(d) *Perlèche* —This type of intertrigo affects the angles of the mouth The base is bright red, the surface may show a pellicle of skin, and fissures commonly develop. Some cases of perlèche are said to be due to infection with Streptococcus Avitaminosis may be a predisposing factor

(e) *Asymptomatic gastrointestinal form* —The presence of C albicans

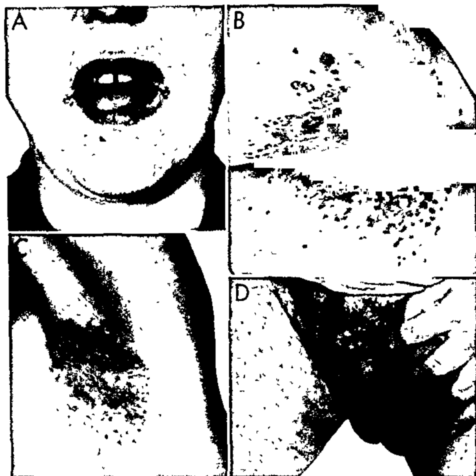


Fig. 65 Candidiasis. A, intertrigo of lips (perlèche), there is often confusion with avitaminosis B, inframammary intertrigo C, axillary intertrigo D, inguinal involvement (D, *courtesy of Dr Royal Montgomery*)

in saliva or in the stools of patients with no symptoms referable to this organism and with no concomitant involvement of the skin suggests that many persons are carriers. With many forms of moniliasis of the skin, organisms can also be located in the gastrointestinal excreta. In the treatment of perlèche, cure is often difficult unless the mouth is treated at the same time.

(*f*) *Intraoral thrush.*—Thrush is seen most commonly in infants and sometimes in babies only a few days old. A whitish, loosely adherent membrane is attached to the inner surface of the cheeks or to the palate and sometimes to other portions of the oral mucosa

(*g*) *Superficial glossitis*—This is manifested by a beefy-red, smooth, and sometimes mottled or enlarged tongue. Stomatitis often is associated.

(*h*) *Water bed dermatitis.*—Kumer and others noted that many patients acquired an eruption when kept in continuous baths, when wet applications of bland nature were applied over long periods, or occasionally when occlusive dressings were left on a part for a considerable time The affected skin is macerated and peels off, a red base may be noted, and satellite vesicopustules may be present. It is to be noted that other yeast-like microorganisms may be present, and, like C albicans, they may be living a solely saprophytic existence.

(*i*) *Eczema*—White and others have noted the occurrence of yeast-like organisms in cases of typical infantile eczema. There is some doubt as to whether C. albicans is able to cause this type of response. Many instances of secondary cutaneous thrush (in children) or of moniliids may be mistaken for eczema.

(*j*) *Vaginitis*—The finding of C albicans in the vagina does not necessarily denote more than saprophytic residence. There is little doubt, however, that the organism may produce vaginitis, with a low grade inflammatory response accompanied by a thin discharge Pregnancy and diabetes are considered to be important conditioning states Pruritus may be a troublesome symptom Rubbing and scratching often lead to secondary pyogenic infection and eczematization, either or both of which may become sufficiently severe to mask the original infection of the vagina.

(*k*) *Pruritus ani*—In cases of severe itching, when one notes considerable maceration around the anal orifice, C albicans may be the cause

More than one of the localized types of infection may be present in the same patient

2 Moniliids, or levurids—Sterile vesicular lesions on the hands and localized or widespread erythematous, vesicular, exudative patches caused by dissemination through the blood stream of products of C albicans have been described by Ravaut and others According to Hopkins, certain cases of miliaria are due to C albicans The condition is probably a moniliid, although Hopkins found the organism in some of the lesions

A focus may be found elsewhere on the skin, but according to Hopkins the gastrointestinal tract is a frequent site. The diagnosis of moniliid of



Fig 66. Moniliosis of generalized type There are discrete flat pustules, exudative inflammatory patches (suggestive of seborrheic eczema), perlèche, beefy tongue with membranous plaques, and diffuse loss of hair on scalp and eyebrows Fingers, toes, and other parts of body were also affected (*Courtesy of Dr Wilbert Sachs*)

the hands is similar to that of trichophytid. Sometimes the absence of a fungus focus on the feet will make one suspicious of moniliid (rather than trichophytid).

3. GENERALIZED CUTANEOUS MONILIASIS.—A fortunately uncommon manifestation seen in infants and children is the type in which the hair of the scalp is sparse and the scalp partially inflamed, with perlèche and glossitis present as well as other types of localized infection, particularly paronychia of several fingers The patient also may exhibit widespread eruptions of the glabrous skin. Characteristic flat pustules may be observed in some part of the eruption. The infection may last for many years and be extremely resistant to therapy, and in some instances the outcome may be fatal. Instances of a particularly exaggerated form have been reviewed by Hauser and Rothman, who also reported a case of monilial granuloma. The lesions may reveal histologic changes in the cutis similar to those seen in the deep mycoses. The primary lesions may be highly vascularized papules, some of which may be surmounted by hornlike, pigmented structures Elevated firm plaques covered with crusts may develop. The scalp and face are particularly prone to be affected, while the trunk and lower extremities are often spared.

Pluss and Kados reported the case of a man aged 32 who had multiple superficial lesions of moniliasis and in addition foul-smelling elevated, spongy, papillomatous masses on the feet and ankles considered due to C. albicans although previously diagnosed as dermatitis vegetans As Wilson has emphasized, it would seem desirable to bear in mind that C albicans is an opportunist and that when unusual clinical pictures are encountered the infection is usually superimposed on some other pathologic disorder. The condition known as acrodermatitis enteropathica was first described by Danbolt and Closs in 1943 as due to a food deficiency, since it appears almost always in infants after the change from breast to bottle feeding. The skin lesions are identical in location and type with those of generalized moniliasis There are perlèche, paronychial swellings, and nail deformities, flexural, circumorificial, and intertriginous, red, vesiculobullous, and exudative plaques, and alopecia. Diarrhea, recurrent in type, is usual C albicans may be cultured from all cutaneous sites and from the stool There is a dejected attitude (Hodgson-Jones). The patient's general health suffers, and the course is usually retrograde, with a poor ultimate prognosis The interesting and so far unexplained feature is a favorable response to administration of diiodohydroxyquin (Diodoquin) This drug has been given orally in doses up to 600 mg four times daily Several weeks or months may be required to obtain definite improvement

It would seem that acrodermatitis enteropathica should not be considered a disease entity until some etiologic agent other than C albicans is established.

4 SYSTEMIC MONILIASIS.—Rockwood and Greenwood and others have reported instances of fatal systemic infection This may be superimposed

on the types just discussed Involvement of the meninges has been described. In some instances bronchitis has been considered to have a monilial source. The finding of Candida in the sputum in cases of suspected bronchial moniliasis is not sufficient to establish a definite diagnosis, since the organism is often present in the mouth and in the gastrointestinal tract

There are no characteristic features of moniliasis of the lungs to distinguish it from other pulmonary mycoses. The disease may be acute but more frequently is subacute or chronic. A productive cough, occasionally hemoptysis with fever, sweats, and progressive loss of weight are common symptoms When repeated tests for the tubercle bacillus have been fruitless, a mycotic disorder should be suspected. A roentgenogram revealing [illegible]

doubt specimens for culture should be obtained after bronchoscopic study. Absence of all other possible causes and a culture reported positive for C. albicans are sufficient to establish the diagnosis It should be remembered that yeastlike fungi are notorious secondary invaders, their presence in diseased tissue does not always mean that they are responsible for the disease The presence of C. albicans in diseased tissue is not always sufficient evidence of its pathogenicity, and in some cases the cause of the condition is difficult to ascertain. It is often necessary to study a patient for some time before a definite diagnosis can be made. Castellani described monilial bronchitis affecting tea tasters of Ceylon. This is a relatively banal infection, with periodic flare-ups of a productive cough lasting for years but finally disappearing spontaneously More severe infections of bronchopneumonic type are uncommon A presumptive diagnosis is in order after repeated examinations (including gastric washings) have been negative for tubercle bacilli if massive amounts of the fungus are observed in the sputum on several occasions Joachim and Polayes reported the case of a white man, 48, who had been addicted to the use of morphine and heroin for 20 years For 18 months he injected the drug intravenously Systemic manifestations developed, and he finally died of subacute endocarditis A species of Candida was obtained in blood cultures and from vegetations on the heart valves Wikler and his associates also reported the case of a drug addict who died of mycotic endocarditis, the organism being C parapsilosis

DIFFERENTIAL DIAGNOSIS

Usually, little difficulty is encountered in recognizing the localized forms of moniliasis and distinguishing them from similar disorders Intertrigo of the feet may occasionally be puzzling, and areas of widespread involvement, especially if they have been overtreated, may be difficult to

recognize at first. Pyodermic infection and tinea due to Trichophyton are easily distinguished by the acute painful paronychia associated with the former and by the lack of paronychia and the presence of a yellow friable nail with the latter. The moniliids are not as definite an entity as one would desire, and the diagnosis must be ascertained by the exclusion of other diseases. Severe generalized involvement should not be confused with any other disorder, although in some instances it is mistaken for seborrheic eczema and there may be a slight resemblance to disseminated neurodermatitis (atopic eczema). The greasy scales of the former and the lichenification present in some areas of the latter, together with the lack of flaccid vesicopustules and negative results of cultural studies, should be sufficient to distinguish these diseases.

In the granulomatous form, there may be a superficial resemblance to bromoderma. The Oidiomycin test is of no value in differential diagnosis. Demonstration of the organisms in culture from lesions of moniliasis is usually readily accomplished. As mentioned previously, tuberculosis must be distinguished from monilial bronchomycosis.

PATHOLOGY

It is advisable to scrape the biopsy material for culture. Mycelium is sometime demonstrable in section, but a diagnosis on this finding alone is impossible. The appearance is usually that of a chronic inflammation, with round cells and occasional giant cells In the granulomatous form, the epidermis is hyperkeratotic and acanthotic. The infiltrate in the cutis is polymorphous, with polymorphonuclear leukocytes, lymphocytes, plasma cells, and occasional giant cells The walls of the blood vessels are thickened.

MYCOLOGY

1 DIRECT EXAMINATION —In material from some untreated lesions, such as those of thrush or erosio interdigitalis blastomycetica, a tangled network of fine mycelium with clusters of spores may be noted In scrapings from nails and many other locations, only a few hyphae or budding cells may be observed, and frequently the results from the potash preparation are uncertain

2 CULTURAL CHARACTERISTICS —The primary growth on dextrose agar is moderately fast and is first noted after two or three days It is wet, pasty, and cream-colored The surface is usually smooth except near the

tree It is notable that pure cultures are the rule It seems that there is marked inhibition of other microorganisms in the presence of C albicans. George and Plunkett have shown that repeated subcultures may produce a



Fig 67 ***Candida albicans*** Direct mounts show filaments and clusters of buds **A**, from macerated skin of groin, × 450, **B**, from edge of infected fingernail, × 450, **C**, from erosion on finger web, × 600, **D**, from oral lesion (thrush), × 600 **E**, young primary culture **F**, giant colony with pasty appearance and craters in center **G**, direct mount from culture with variations in size of cells, × 1 200 **H**, development of chlamydospores and filaments on cornmeal agar, × 450

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MYCOLOGY

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2. Cultural characteristics —The primary growth on dextrose agar is moderately fast and is first noted after two or three days It is wet, pasty, and cream-colored The surface is usually smooth except near the center of the colony, where it has a honeycombed appearance due to ruptured air bubbles On cornmeal agar, a deep stab with a needle containing the cultural growth results in the characteristic picture of an inverted pine tree It is notable that pure cultures are the rule It seems that there is marked inhibition of other microorganisms in the presence of C albicans George and Plunkett have shown that repeated subcultures may produce a

lesion of the skin or of the gastrointestinal tract is there a positive response to the intracutaneous test with a commercial extract of C. albicans. Of patients without any obvious infection, from 46 to 54 per cent have a similar positive reaction. With increasing age, the percentage of reactions to the test increases, thus in the decade between 51 and 60 years, inclusive, 75 per cent of apparently normal persons show a cutaneous reaction to the injection of an extract of C. albicans. For these reasons, the Oidiomycin test is of little help as a diagnostic procedure.

PROGNOSIS

Patients with any form of moniliasis should be considered potentially diabetic. The infection may be the first manifestation of diabetes. The local varieties usually respond to treatment, but relapse may occur. It is difficult to eradicate the microorganism from the gastrointestinal tract Generalized involvement and moniliids are resistant to therapy, and cure may require months or years. When infection is generalized, particularly with the granulomatous form, the prognosis should be reserved, in cases of systemic involvement the outcome is often fatal

TREATMENT

1. General instructions —If it is to be comprehensive and permanently effective, therapy should be directed toward the eradication of all foci, both in the skin and in the gastrointestinal tract. Unfortunately, treatment of the latter is not highly effective. Infection caused by C albicans calls for urinalysis to determine whether an otherwise asymptomatic glycosuria is present. Blood sugar tolerance tests are often advisable

The treatment of infections of the skin caused by C. albicans depends partly on the site of the disorder and partly on the individual patient. When the hands are affected, it is important to keep them from frequent immersion in water The use of cotton and rubber gloves may protect them to some degree Improvement in hygiene may be helpful in preventing the development of lesions Multivitamin supplement to the diet is indicated We have not had much success with low-caloric diets Most of our patients will not submit to the necessary discipline in order to reduce their weight

Hopkins noted that a patient with generalized cutaneous moniliasis and with involvement of the gastrointestinal tract improved while on a diet free from bread, cereals, potatoes, and other starchy vegetables and with dextrose instead of cane sugar. Magnesium carbonate and calcium carbonate were given in large doses.

2 Local treatment —Churchman introduced methylrosaniline chloride (gentian violet) as effective in the treatment of infections caused by Gram-positive organisms Gomez-Vega noted that the growth of organisms of the genera Monilia and Torula, when tested in vitro, was inhibited in

rough, dry colony. Weld described a spidery or feathery mycelial growth recognizable within 18 hours when C. albicans is grown in atmosphere containing 10 per cent carbon dioxide.

3. CULTURE MOUNT.—Mycelial development is best seen in material from colonies grown on cornmeal or Nickerson's agar. Clusters of spores in rounded masses are to be observed along the hyphae, and, diagnostically, chlamydospores also develop No ascospores are present. As George and Plunkett have shown, the mycelium becomes much branched and bushy, while blastospores and chlamydospores may be reduced, in some strains repeatedly subcultured over a long period.

4. BIOPSY OF CULTURE.—There is no fringe. The core is well established in a broad band, breaking up into clusters in the younger and older fields Strands of mycologic material, staining less densely, are noted in the substrate On high power study, the fungus material is seen to be composed almost entirely of budding round cells considered to be blastospores Only a few lightly staining hyphae are present. Chlamydospores may be readily demonstrated in the substrate.

5. FILTERED ULTRAVIOLET RAYS.—The appearance of a colony changes little from its appearance in normal light, the color is clear, dull, and yellowish brown.

6. ANIMAL INOCULATION —Intracutaneous inoculation in guinea pigs causes a mild inflammatory reaction. Rabbits are killed by the intravenous injection of 1 cc. of a 1:1,000 suspension, miliary abscesses being produced in all parts of the animal (Benham).

7. FERMENTATION REACTION —Acid and gas are produced with dextrose, levulose, and maltose but not with saccharose (Benham).

8 AGGLUTINATION REACTION.—Agglutination is seen when a serum is prepared against a known strain of the yeast (Benham)

9 COMPLEMENT FIXATION.—This may occur from a patient's serum and Candida

10 DIFFERENTIAL DIAGNOSIS (LABORATORY) —Cryptococci do not develop mycelium, and other fungi in the Candida group may be distinguished from C albicans by the absence of chlamydospores when they are grown on cornmeal agar Mycoderma may usually be recognized by its gross appearance in culture, a culture mount reveals arthrospores Endomyces and Saccharomyces form ascospores, the former also develops mycelium.

In culture biopsy, the finding of thick-walled, uniform-sized blastospores with a few filaments indicates a yeastlike growth. The presence of chlamydospores in the substrate is confirmatory

IMMUNOLOGY

In only 57 per cent of patients with the localized form of cutaneous moniliasis and in only 52 per cent of patients harboring the organism in a

5 Vaccine therapy.—There are not many reports in the literature regarding the efficacy of this form of therapy. Sulzberger and Wise and later Kerr, Pascher, and Sulzberger reported successful quantitative intracutaneous therapeutic desensitizations with Trichophyton and Candida extracts, alone and in combination Olah tried autovaccine therapy without success in cases of onychia and paronychia.

In a series of 48 cases, we used intracutaneous injections of Oidiomycin. The patients received from six to 44 injections, the average number being 11. The vaccine was administered in dilutions of 1·1,000 to 1:500, 1·100, and 1 50, beginning with the more dilute and proceeding to the more concentrated doses. The patients were given a bland application for topical use, for the most part a colored petrolatum. No absolute cures were noted, but there was an apparent improvement in the condition of a few of the patients. In the great majority of cases no improvement was noted. In no case was there any harmful complication, such as an exacerbation of the eruption or a focal reaction

6 Other measures.—When the infection is severe, attention to the general health and measures to build up bodily resistance, such as vitamin therapy, a nutritious diet, and added rest, may be of primary importance. Nystatin (Mycostatin), mentioned above, may also be prescribed.

In the treatment of Candida infection of the nail the patient should be told to avoid soaking the hands in water, particularly with soap, to avoid the peeling of unwashed vegetables, and to dry the skin carefully after washing the hands. If possible, a housewife should arrange to do all the scrubbing or washing at one time of the day Roentgen therapy may be used. [illegible]
base c [illegible]
stick [illegible]
paronychial tissues once daily. Boric acid ointment and sodium perborate paste are other useful topical remedies

In the bronchopulmonary and pulmonary forms, potassium iodide should be administered in ascending doses over prolonged periods In some cases there seems to be an advantage in employing ethyl iodide by inhalation Gentian violet, intravenously, has been advocated by Stovall and Greeley Reports by Kass, Sasanom and Klein, and Smith and Armen indicate a favorable effect from inhalations of brilliant green in aerosol This is a nontoxic preparation and inexpensive.

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dilutions of 1:1,000,000 of gentian and methyl violet. Cornbleet found gentian violet more effective when followed by an application of Gram's solution of iodine. Aqueous solution of gentian violet 1 to 2 per cent is probably still the best single topical remedy against Candida infections of the skin. It may also be used in the treatment of oral thrush. We have used it with success in suppositories (2 grains, or 0.13 Gm., to each) in the treatment of monilial vaginitis and pruritus ani due to C. albicans. The chemical may also be incorporated in zinc paste Sutton has written a comprehensive article on the uses of gentian violet in dermatology.

Nystatin (Mycostatin), an antibiotic, is only feebly effective when incorporated in an ointment base for local application. Its chief use appears to be in its administration orally for its inhibitory action on Candida in the gastrointestinal tract. Nystatin may be administered to infants in a flavored powder, the dose being 100,000 units three times daily. For older patients a tablet containing 500,000 units may be given three times daily. Tablets for vaginal insertion are available in a dose of 100,000 units.

Many other advocated local remedies are useful in certain instances Wet dressings are almost always well tolerated and are often an acceptable means of beginning treatment A solution of 1:2,000 potassium permanganate or a 1 5,000 solution of perchloride of mercury applied for a few days in continuous wet dressings to areas of local infection often brings about considerable clinical improvement Sodium perborate as a mouthwash and a 1 per cent solution of silver nitrate in nitrous ether in many instances of monilial intertrigo have proved of value Ormsby recommended tincture of iodine 1 per cent or half strength Whitfield's ointment. Mercurial preparations, such as ammoniated mercury ointment (3 to 10 per cent), are more effective against Candida than against the dermatophytes Soothing applications, such as zinc oxide lotion or wet compresses of boric acid, are sometimes necessary when acute inflammation is present

3 Roentgen therapy —Roentgen rays are useful in the treatment of paronychia and onychia and are also sometimes effective in the treatment of perlèche The usual dose is 75 r administered without filtration once weekly for four to six treatments

4 Treatment with iodides —There is sometimes help from the administration of potassium iodide by mouth in the treatment of the localized forms of moniliasis In some instances we have given the medication to the point of evidence of intolerance The results are often equivocal, and only small doses are advised Strong iodine solution (Lugol's solution) diluted one-half with water is a nonirritating application which we have used successfully in the treatment of oral thrush as well as in other types of moniliasis In an apparently hopeless case of the systemic type of moniliasis observed by MacKee, C albicans was isolated from the skin, gastrointestinal tract, and sputum Treatment by topical applications of gentian violet together with systemic iodides resulted in marked clinical improvement In such cases iodides should be given in ascending dosage up to tolerance (*see* Chapter 28)

14. Tinea Versicolor

TINEA versicolor, also known as pityriasis versicolor and chromophytosis, is a common superficial mycosis of world-wide distribution, readily recognized and treated. The condition is chiefly of importance cosmetically.

ETIOLOGY

The microorganism causing tinea versicolor is known as Malassezia furfur. The disease affects young adults (of both sexes) by preference, but we have observed instances of infection in children and in the aged While social standing is not important, lack of personal hygiene, commoner in the dispensary patient, predisposes to infection. Some persons appear to be susceptible without apparent reason Hyperhidrosis is thought to encourage the infection and may explain the high incidence in the tropics. Several members of a family may be infected. Contrary to an old belief, the disease is not commoner in patients with pulmonary tuberculosis. The more usual physical examination of such persons probably led to the discovery of the disease, and its equally frequent inhabitation of the skins of other persons was not realized. Patients with the disorder are usually seen in warm weather, when its presence is more evident.

CLINICAL CHARACTERISTICS

1 USUAL SYMPTOMS —The incubation period is said to be one month (Darier) The disease manifests itself by scaly macules and patches starting from barely visible lesions in single or multiple foci. The color varies from that of the skin to dark brown It is said that the usual color is yellowish fawn, but the shade varies with the season During the winter the color may be that of the skin or light brown In the summer, particularly toward the end, the color becomes darker and may be of a chocolate shade. Usually no inflammation is evident The surface of the affected skin is sometimes noticeably scaly, but often a scratch is necessary to dislodge the scales

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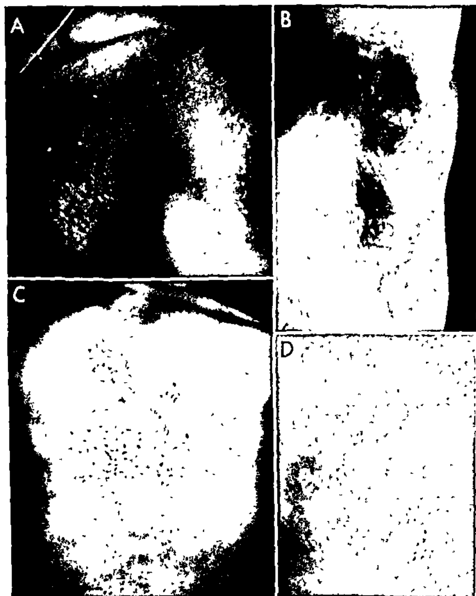


Fig. 68. Tinea versicolor, or chromophytosis Superficial scaly macules and plaques in

skin

Cases of follicular involvement are rarely observed. In such cases the lesions remain small and may become slightly elevated. The sites of predilection are the chest, the abdomen, and the back, but the condition may attack any part of the skin, including the scalp and the palms and soles Baer noted an instance of involvement of the face and scalp. We have observed a number of instances of infection on the back of the neck, and the extensor surface of the arm above the elbow appears to be a common site. *At times the eruption favors intertriginous locations, such as the* axillae, the inframammary folds, or the inguinal regions, adiposity may predispose to involvement of these regions. The disease sometimes affects large sheets of skin, and the manifestations may be extreme. Mild itching may be present. There is little if any tendency to spontaneous cure

2. Pseudoachromia.—During the summer or autumn, a patient with tinea versicolor not uncommonly exhibits light-colored (apparently depigmented) areas on the surfaces of skin exposed to sunlight. These areas usually appear suddenly after sunburn followed by peeling, although a history of a visible reaction is not always obtained. The patches occupy the sites of lesions of tinea versicolor; they are irregular and of various sizes and appear chiefly on the trunk. Their color is not the dead white of vitiligo, although because of their contrast to the surrounding skin, especially in persons of dark complexion, they may be mistaken for that disease Areas of skin on the covered parts of the body are usually found to match in color the achromic-appearing spots. There is no increase of pigment at the periphery of a lesion. A scarcely perceptible scaling may be noted. Sometimes the condition appears year after year, becoming less noticeable during the winter and reappearing during the summer.

The light areas do not, as a rule, become tanned after further exposure to ultraviolet radiation, on the contrary, they become more and more noticeable, owing to the increase of pigment in the surrounding normal skin. Patients almost invariably discover for themselves that sunlight produces this undesirable effect

Examination for fungi combined with observation of the patient under filtered ultraviolet rays reveals that organisms are frequently present in these light patches Some writers have expressed the opinion that there is definite achromia Our inquiry into the nature of the lightening of the skin favored the theory of mechanical screening of the sun's rays, suggesting that the skin was light by contrast to the surrounding, normally pigmented skin A mechanical cause was indicated by the facts that (*a*) the dopa reaction revealed a normal amount of pigment in the skin, (*b*) the scales of tinea versicolor protected the skin from ultraviolet rays to a greater degree than the scales of psoriasis or of pityriasis rosea, (*c*) fluorescent material from cultures of other fungi possessed a screening effect against ultraviolet radiation, and (*d*) increase in pigment in a patch was possible only when the overlying microorganism had previously been treated and destroyed.

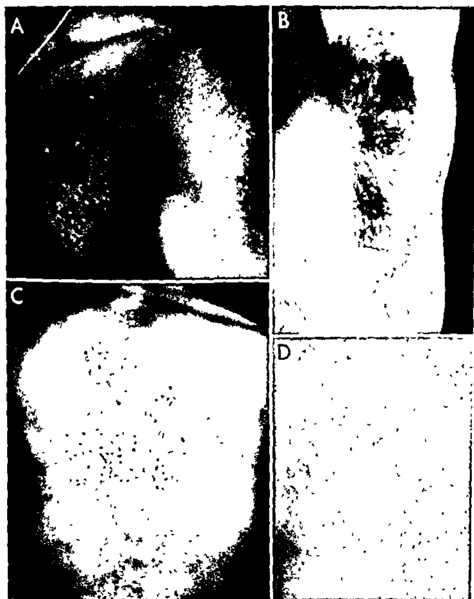


Fig 68. Tinea versicolor, or chromophytosis Superficial scaly macules and plaques in typical locations Color varies with season being darker in summer and lighter during winter In **A**, there are numerous small areas scattered over upper chest and shoulders Tendency in **B** is for confluence into irregularly-sized lesions in region of axilla More usual picture is portrayed in **C** In **D**, color of patches is light in comparison with normal skin

DIFFERENTIAL DIAGNOSIS

The ordinary form of tinea versicolor is rarely confused with any other disease. If of limited extent, it may simulate chloasma. Since the organism can be readily demonstrated and since the appearance under filtered ultraviolet rays is characteristic, there should be no mistake. In erythrasma, the disorder is limited to the armpits and groin; the color is usually darker and the scaling more profuse than in tinea versicolor. The coral fluorescence at the periphery of the patch is also diagnostic.

With pseudoachromia of tinea versicolor, certain other diseases may be considered.

1 ACHROMIE PARASITAIRE A RECRUDESCENCE ESTIVALE.—From the published description of Jeanselme it appears that this disease is pseudoachromia of tinea versicolor.

2. ACHROMIA PARASITARIA.—It is difficult to fit together the varied symptoms in the syndrome which Pardo-Castello and Dominguez described. In some cases irregular, dirty-white macules and patches which are slightly inflamed, scaly, and somewhat itchy are present on the face and neck. In other cases the eruption is generalized, no inflammatory symptoms are present, and the disorder simulates the pseudoachromia of tinea versicolor. One of the illustrations in the article by Pardo-Castello and Dominguez shows lesions on the trunk which suggest the last-mentioned disease In both disorders, the scaling in the early macules is white and furfuraceous and the older lesions are devoid of scales. There is no increase of pigment at the edges The mucous membranes, hair, and nails are not affected In the series reported by Pardo-Castello and Dominguez there were four cases in which the disorder was generalized, the palms and soles being free. Aspergillus was cultured in six of 36 cases and was considered a possible cause of the disease No mention was made of examination of scales in potassium hydroxide for the presence of M. furfur In a later communication, Pardo-Castello expressed his belief that the same clinical picture may be found in patients of different races and in persons residing in different countries, that it may affect different types of persons, and that it may be caused by a variety of organisms. He did not believe that the rays of the sun play any part in the cause Further investigative work appears necessary to clarify the picture.

3 TINEA FLAVA, OR TINEA VERSICOLOR TROPICALIS —Castellani stated that this condition is identical with achromia parasitaria (Pardo-Castello and Dominguez). The fungus responsible cannot be distinguished from M. furfur in potassium hydroxide preparations, and like that organism it is nonculturable Castellani differentiated tinea flava from tinea versicolor as it occurs in the temperate zones by the following points (1) Tinea flava begins in childhood and may persist throughout life (2) It usually affects the exposed parts of the body. (3) Cure is difficult. (4) The fungus seems to have a marked depigmentary action

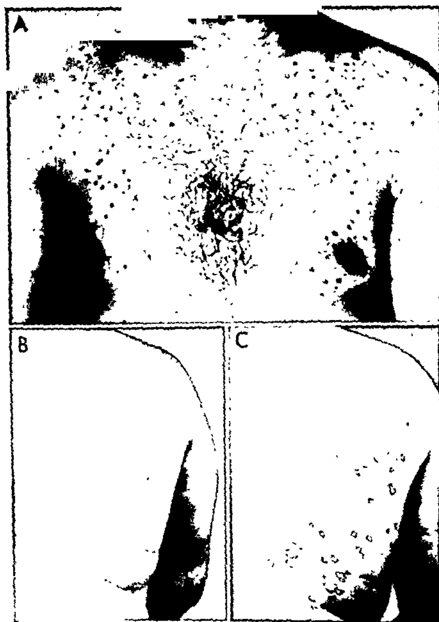


Fig 69 Tinea versicolor A, patient with lesions of tinea versicolor over chest and erythrasma in the axillae Coral fluorescence of erythrasma is distinctive B, clinical appearance of patient during winter months, showing no infection C, same patient with lesions of tinea versicolor outlined as revealed under filtered ultraviolet rays

DIFFERENTIAL DIAGNOSIS

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3 Tinea flava, or tinea versicolor tropicalis —Castellani stated that this condition is identical with achromia parasitaria (Pardo-Castello and Dominguez) The fungus responsible cannot be distinguished from M furfur in potassium hydroxide preparations, and like that organism it is nonculturable Castellani differentiated tinea flava from tinea versicolor as it occurs in the temperate zones by the following points (1) Tinea flava begins in childhood and may persist throughout life. (2) It usually affects the exposed parts of the body (3) Cure is difficult (4) The fungus seems to have a marked depigmentary action



Fig 70 Tinea versicolor. A, papular follicular variety, rarely observed, B and C, pseudoachromia caused by screening effect of lesions during exposure to ultraviolet rays This may be mistaken for vitiligo D, papular, and in part follicular, highly pigmented lesions

4. ENDEMIC VITILIGO OF TURKESTAN.—According to Kistiakovsky, who has observed the disease, there is no difference between this disorder and vitiligo.

5. PINTA.—When this condition is observed early, the characteristic hues of the affected skin in no way suggest tinea versicolor. Later, when vitiliginous areas are present, differentiation may be more difficult. The disease causes coarse scales, the affected skin is infiltrated, occasional fissuring is noted, and loss of hair is usual. When extensively involved, the skin presents an odd, piebald appearance

6. SYPHILITIC LEUKODERMA —This condition is seen almost exclusively in women. The lesions are commonly symmetrically located on the sides and back of the neck, are oval or irregularly shaped, and vary from the size of a split pea to that of a dime. Concomitant hyperpigmentation is sometimes noted. No scaling is present. Other evidence of syphilis, including a positive serologic reaction, can usually be detected.

7. VITILIGO.—The irregular, asymmetric, snow-white patches, showing hyperpigmented edges and affecting by preference the face, hands, forearms, and male genitalia, should not often prove difficult to differentiate No scaling is present. Vitiliginous skin observed under filtered ultraviolet rays has a characteristic fluorescing, glistening-white appearance. It must not be forgotten that patients with tinea versicolor may also have vitiligo. This unrelated association is the probable explanation for the absolute achromia reported by a few observers and thought to be consecutive to the pigmented rash of tinea versicolor.

8 POSTERUPTIONAL DEPIGMENTATIONS. — Seemingly depigmented areas may be noted at the former sites of syphilitic, psoriatic, and other cutaneous lesions Without any history of a preceding eruption, differential diagnosis may be difficult

As with the ordinary form of tinea versicolor, diagnosis requires microscopic studies reinforced by studies with filtered ultraviolet rays

MYCOLOGY

1 DIRECT EXAMINATION —The facility of diagnosis is rarely approached with specimens from any other mycosis The scales may be examined as soon as the potash preparation is made There is usually an abundance of material consisting of spherical or ovoid refractile spores in groups or clusters Mycelium is seen in considerable numbers as wavy threads of moderate length Branching may be noted The filaments are readily broken up when one is making the mount When scales are removed from the surface of patches of pseudoachromia, only a few spores, without appreciable grouping, may be noted Filaments are usually few, they consist of short rods Cohen has described a simple staining technique in which a drop of Parker 51 superchrome blue-black ink is added to the KOH preparation Porto has added another method in transferring

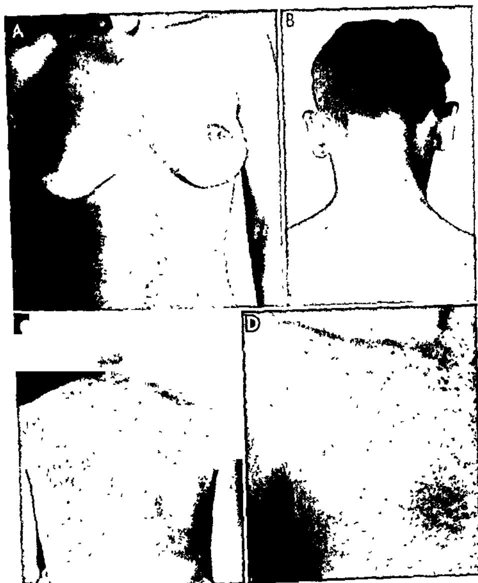


Fig 70. Tinea versicolor. A, papular follicular variety, rarely observed, **B** and **C,** pseudoachromia caused by screening effect of lesions during exposure to ultraviolet rays This may be mistaken for vitiligo **D,** papular, and in part follicular, highly pigmented lesions

the scales and pressing the material on the microscopic slide through the medium of cellophane (Scotch) tape.

2 Cultural characteristics —A number of investigators have reported success in culturing the organism, but so far there is no general agreement. Gordon grew out a spherical organism, which he named Pityrosporum orbiculare. Inoculation of this fungus in human beings and laboratory animals failed to reproduce the disease. Moore described experiments in which he obtained cultural growths on many different media after the initial isolation on maltose broth. He was able to inoculate three of eight human volunteers when no laboratory animal was susceptible. In addition to the necessity of proving that a given culture is pathogenic for animals or for human volunteers, it appears essential to demonstrate fluorescence under filtered ultraviolet rays of the cultural growth and of the lesions experimentally produced.

3. Filtered ultraviolet rays.—When lesions of tinea versicolor are examined under filtered ultraviolet rays, fluorescence is noted, this varies from golden yellow to dark brown (depending on the amount of pigment in the lesions). This fluorescent characteristic has proved of interest and value not only in establishing a diagnosis but in determining the extent of the eruption Changes in the color of the skin may be invisible in ordinary light but will be readily detected when a thorough cutaneous inspection under filtered ultraviolet radiation is undertaken. The appearance of the cultural growth is unknown.

4. Animal inoculation —Ordinary laboratory animals appear immune to the fungus applied in scales. Cultural growths would be essential to a decision on this point. The disease has not been reported as occurring naturally in any domestic, wild or laboratory animal

5 Differential diagnosis.—The presence of clusters of spores (apparently with double-contoured walls) and of fragmented mycelium (usually abundant) provides a characteristic picture In C. albicans the filaments are more slender and dense masses of spores (sometimes budding) are a distinguishing feature.

IMMUNOLOGY

There is no acquired sensitivity to trichophytin. The cultivation of M furfur is still a matter of conjecture, specific sensitization to a vaccine therefore remains to be proved Since the process is superficial and no involvement of the cutis is to be observed, sensitization is unlikely.

PROGNOSIS

The outlook for complete cure is good if treatment is thorough Reinfection will occur if the patient is re-exposed, since immunity is not produced by an attack



Fig 71. Malassezia (Microsporum) furfur. A, stained preparation (Schiff) showing short filaments and groups of spores with double-contoured walls, × 750 Note occasional budding B, section through skin with organism in follicle, × 680

TREATMENT

The extent of the eruption should be determined by examination of the entire cutaneous surface under filtered ultraviolet rays, and the patient should be advised to treat all parts that show fluorescence If all the affected areas are treated, improvement will be rapid.

It is advisable that all family contacts be examined and, as in the treatment of scabies, that all members affected should concurrently receive therapy It is important that clothing be cleaned, if possible by washing, although dry cleaning will suffice

After two weeks, and subsequently when he visits, the patient should again be observed under filtered ultraviolet rays Areas which have escaped medication will be revealed. Scrapings taken from suspected areas will yield either positive or negative information

We stress the principles of treatment rather than the medicaments to be used A 10 per cent solution of sodium hyposulfite sponged on once daily before the patient retires is the usual medicament; another useful application is 1 per cent tincture of iodine However, almost any exfoliant or fungicide will prove effective, but overtreatment dermatitis should be avoided A hot bath previous to application of the remedy is helpful. Therapy should be continued for at least two weeks after all evidence of the disease has disappeared.

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15. Erythrasma

ERYTHRASMA is a superficial mycosis resembling tinea versicolor but with more tendency to intertriginous localization Burckhardt first described the disease in 1859.

ETIOLOGY

The causative fungus is a minute threadlike microorganism, Nocardia minutissima Little is known concerning predisposing causes or methods of transmission of the infection. Lack of cleanliness may be a factor. The disease is less common in the United States than in Europe It is seen much less frequently than tinea versicolor.

CLINICAL CHARACTERISTICS

The patients are usually young adults, men more commonly than women Localization to the axillae, the groins, the intergluteal cleft, or other intertriginous areas, with involvement of one or more regions, is characteristic. The disease begins as small scaly macules which gradually enlarge to form various-sized patches The lesions are well circumscribed, the margins being accentuated by a reddened border The color varies through yellowish brown, orange, and reddish brown, the exact shade depending on the amount of pigment in the skin of the subject, the age of the lesion (the older the darker), and the amount of solar radiation to which the lesions have been subjected The surface of the lesions is scaly Vesicles, papules, and follicular lesions are not present

DIFFERENTIAL DIAGNOSIS

In tinea versicolor, there is less tendency to localization in intertriginous areas and there is no erythematous border When the inner surfaces of the thighs, the inguinal region, or the pubic area is affected, tinea cruris may be simulated The long duration, the lack of inflammation (especially

TREATMENT

The extent of the eruption should be determined by examination of the entire cutaneous surface under filtered ultraviolet rays, and the patient should be advised to treat all parts that show fluorescence If all the affected areas are treated, improvement will be rapid.

It is advisable that all family contacts be examined and, as in the treatment of scabies, that all members affected should concurrently receive therapy. It is important that clothing be cleaned, if possible by washing, although dry cleaning will suffice.

After two weeks, and subsequently when he visits, the patient should again be observed under filtered ultraviolet rays Areas which have escaped medication will be revealed Scrapings taken from suspected areas will yield either positive or negative information

We stress the principles of treatment rather than the medicaments to be used A 10 per cent solution of sodium hyposulfite sponged on once daily before the patient retires is the usual medicament, another useful application is 1 per cent tincture of iodine. However, almost any exfoliant or fungicide will prove effective, but overtreatment dermatitis should be avoided A hot bath previous to application of the remedy is helpful. Therapy should be continued for at least two weeks after all evidence of the disease has disappeared

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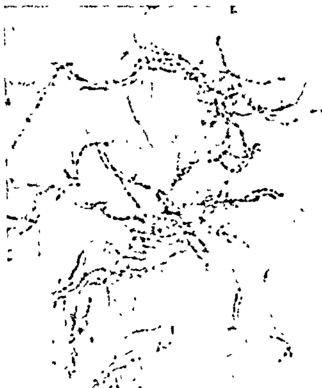


Fig. 73. Nocardia minutissima Stained slide showing interlacing filaments (oil immersion, × 1,800).

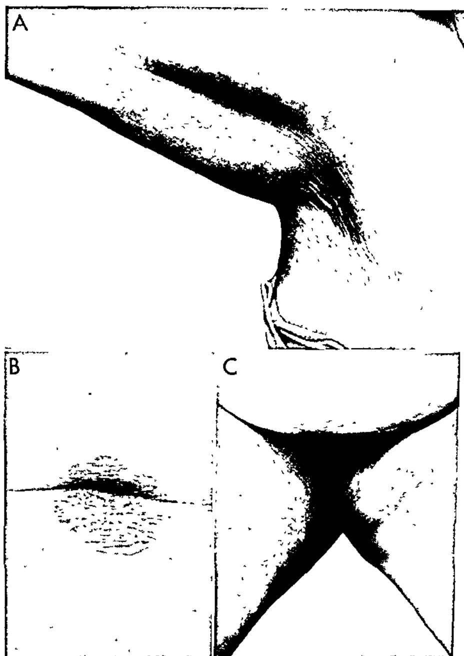


Fig 72 Erythrasma Process is usually localized and well demarcated **A**, in and near axilla **B**, region of umbilicus **C**, upper inner thighs and inguinal region

the sar a 10 per cent aqueous solution of sodium An ointment containing salicylic acid 2 per cent may be preferred. Daily bathing should be advised to prevent reinfection.

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of a vesicular border), and the absence of satellite lesions tend to rule out tinea cruris.

Demonstration of the causative microorganism is much more difficult than with tinea versicolor.

MYCOLOGY

1. Direct examination.—The scales may be examined after preparation in 10 per cent KOH to which a drop of methylene blue has been added. The fungous elements are too small to be seen under the usual low power magnification. Under high power magnification one may make out fine threads. *On examination with the oil immersion lens, the threads appear* long, tortuous, and interlacing; segmentation may be noted. A few round spores may be seen. Granules are occasionally visible.

2 Cultural characteristics.—We have not been able to grow the organism on artificial mediums. According to Poehlmann, however, several investigators have been able to do this

3. Filtered ultraviolet rays —The rash caused by this microorganism has a distinctive bright-coral fluorescence. According to Michaelides and Shatin:

> A characteristic bright-red fluorescence has been seen only in the lesions of erythrasma but not in all of these. The red fluorescence, when present, may correspond to the entire erythrasma lesion, may form a border at the edge of the lesion, or may form patches within the lesion. In each case the fluorescence appears only within the limits of the erythrasma lesion, but does not necessarily occupy the whole of the lesion Wherever there is fluorescence, one can find the organism by microscopic examination

4. Animal inoculation.—We have not had any personal experience with this.

5 Differential diagnosis (laboratory).—The microorganism is so small that it may be mistaken for an incidental bacterial contaminant. No other species of fungus can be confused with it

IMMUNOLOGY

There is no sensitization to trichophytin. Sensitization to the cultural organism has been reported, but this is questionable

PROGNOSIS

Provided all areas are treated, relapse is uncommon.

TREATMENT

All areas of infection as noted by a thorough inspection must be treated. All the affected members of the family should receive treatment at

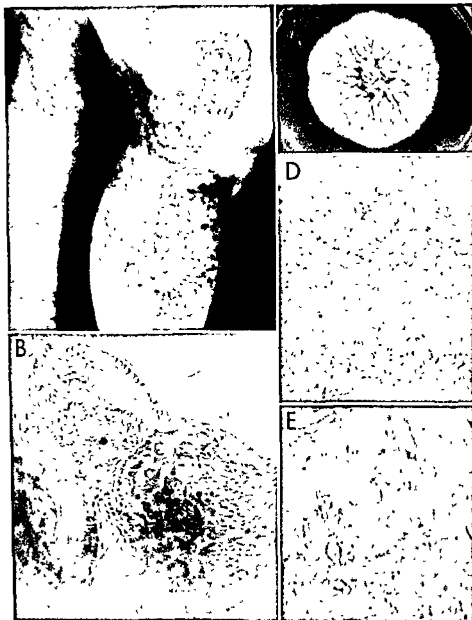


Fig 74 [illegible]
tendency t[illegible]
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Reiss)

16. Tinea Imbricata

TINEA imbricata, a tropical fungous disease caused by *Trichophyton concentricum*, has an extensive geographic distribution, and the clinical features are often characteristic.

HISTORY

The place of origin of the disease is thought to be the Malay Archipelago Its distribution has been traced to follow the migration of the Malay race. The disease was described first in 1789 by Danpier, who observed it affecting inhabitants of the Philippine Islands and of the Marianas (Manson). Alibert gave a good account of the disease in 1832. Walker recognized cases in the Gilbert Islands in 1844. There were a few other reports before Manson's classic discussions of 1879 and 1892. In those reports Manson described clinical details as well as microscopic features of the causative fungus. He mentioned the division of opinion as to its identity, then prevalent, and effectively disposed of the contention of Tilbury Fox and others that tinea imbricata was only a tropical variant of tinea corporis as usually observed in Europe. In 1903 Leme discovered the disease in Brazil In 1918 Pijper reported the first case from South Africa. Other countries in South and Central America were shown to harbor cases by Pinto, DaFonseca, Mora Mora, and others According to Leão, the disease in America dates from pre-Columbian times Most of the patients were Indians living under primitive conditions.

ETIOLOGY

The causative fungus was described by Castellani as belonging to the genus Endodermophyton. He found four species of Endodermophyta—concentricum, indicum, tropicale, and mansoni—to be the pathogens responsible. Most workers believe that these are variants of a single species and classify it as Trichophyton concentricum

As Manson pointed out, the condition is observed in places where the

although some strains may require 37 C. In tubes free from contamination, a few mycelial filaments appear. After several weeks the fluffy mass may be transferred to a solid medium. There is some resemblance to T. schoenleini The growth is compact and gray to brown, with an uneven surface.

3. CULTURE MOUNT.—Vegetative forms are numerous Arthrospores but no microconidia are present.

4. ANIMAL INOCULATION —Reiss and Tshu were unable to inoculate rats, guinea pigs, and rabbits.

5. FILTERED ULTRAVIOLET RADIATION —As in other glabrous growths, the Wood light reveals no characteristic fluorescence.

6. DIFFERENTIAL DIAGNOSIS (LABORATORY).—The filaments are more numerous and are located deeper in the epidermis than those of T. rubrum. The cultural growth is glabrous, and this characteristic, together with the tinctorial and other features, serves to rule out other fungi.

PROGNOSIS

Cure is difficult to attain under tropical conditions. Improvement is usually temporary, and relapse is common.

TREATMENT

Castellani advised treatment with 25 per cent resorcinol in tincture of benzoin, with 5 to 10 per cent chrysarobin in an ointment base, or with iodine liniment Later he advised the use of a paint which contains carbolfuchsin and which has been named after him.

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coconut tree grows. It is fairly common in many of the Pacific islands, in the Malay States, and in central and southern China; cases have also been reported from North China (Reiss), Ceylon, southern India, South Africa, and Central and South America. According to Polunin, no sex or age group is specially susceptible to the disease.

CLINICAL CHARACTERISTICS

The condition begins as one or more brownish spots, which slowly increase in size. The central portion of the superficial epidermis finally becomes detached and the epidermis cracks, forming large flaky scales which remain attached at the periphery. Since the scales are attached along the edge of each ring, roughness is experienced if the palpating finger moves peripherally There is little if any visible redness. The scaly ring grows outward In a week or two a new brown patch appears in the center of the first ring. Eventually it too develops a scale which becomes detached proximally. In a similar manner, additional rings develop. In all, eight or 10 may form, the newest developing within the next newest. In contrast to M canis causing tinea circinata, this fungus never gives up epidermis it has infected Castellani stated that the rings advance at the rate of a quarter to half an inch a week. Other sites become similarly infected, and the entire body may eventually be involved, the anterior scalp apparently being the most resistant site In cases of scalp involvement, the hair follicles are spared. The face is not often affected Castellani stated that nails are vulnerable, but Polunin has never observed infection of nail tissue. Itching is variable and is worse during extremes of heat. When the disease is severe, the regular pattern may disappear and the skin become lichenified.

DIFFERENTIAL DIAGNOSIS

The absence of redness, the profuse scaling, the multiple concentric rings, and the extensive distribution are against a diagnosis of tinea glabrosa due to M canis, T mentagrophytes, or T rubrum In a case reported by Kittredge an eruption similar to tinea imbricata was caused by T. rubrum Ichthyosis is usually present from birth, and the scaling lacks the concentric rings seen in tinea imbricata

MYCOLOGY

1. DIRECT EXAMINATION —Numerous interlacing segmented hyphae are present in scales

2. CULTURAL GROWTH —Scales should be soaked in alcohol for five to 10 minutes and then placed in dextrose broth with penicillin added This procedure cuts down the possibility of bacterial contaminations, which often overrun the fungous growth Incubation at room temperature is usual,

DIFFERENTIAL DIAGNOSIS

Differential diagnosis is usually not difficult to make from the clinical appearance. The concretions, or nodes, exhibit fluorescence under filtered ultraviolet rays. If a hair to which the concretions are attached is examined under a microscope, the mass is seen to extend along a portion of the hair and nits, which are attached at one point only, can be excluded from consideration

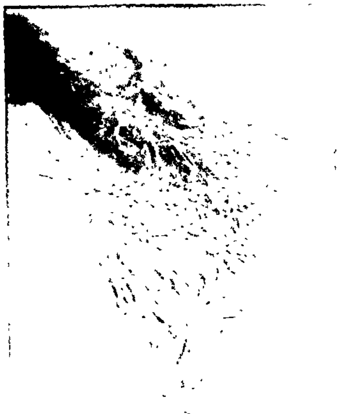


Fig 75 *Trichomycosis axillaris*. Concretions are irregular in size and yellow.

MYCOLOGY (BACTERIOLOGY)

1 Direct examination —In KOH preparations, delicate short rods may be observed throughout the node Clumps of cocci are said to be present in addition in the red and black forms.

17. Trichomycosis Axillaris

(Lepothrix)

IN THE silent disorder trichomycosis axillaris, concretions are attached to hair, chiefly in the axillae, occasionally on the pubis, and rarely in the beard. Recent work suggests that this disease is not of fungous origin. The first account of the disease is credited to Paxton (1869) While commoner in the tropics, the disorder is not unusual in the temperate zone.

ETIOLOGY

Castellani's research seemed to show conclusively that the primary causal microorganism was in the *Actinomyces* or *Nocardia* group. Other investigators found either bacillary, coccal, or branching organisms. Weidman cultured a species of *Actinomyces* from a hairy black tongue. When the fungus was fed to a monkey, lesions of trichomycosis developed on the hair of the face and of the axillae The report of Crissey, Rebell, and Laskas submits sound evidence that a bacterium *Corynebacterium tenuis*, is chiefly responsible, although in the tropics other microorganisms (Micrococci) may be contributory

CLINICAL CHARACTERISTICS

The condition is noted in the axillae, where irregular concretions form along the hair shaft Occasionally the pubic hair is affected The attachment is firm, and the nodes are difficult to dislodge The entire circumference of the hair is ordinarily involved The concretion is usually yellowish, red and black varieties are uncommon in New York but are seen with more frequency in the tropics Hairs on which the nodosities form may become friable but are otherwise unchanged Lack of subjective symptoms and the usually poor color contrast often results in the disease being overlooked.

18. Tinea Nodosa

(Piedra)

PIEDRA is an infection due to one of two fungi and is characterized by white or black firm nodules attached to hairs on the scalp, beard, or upper lip.

HISTORY

The white variety was first described in London by Beigel in 1865. Black piedra was recognized in Rio de Janiero by de Malgoi-Hoes in 1901. Most of the literature on the disease originates in South America.

GEOGRAPHIC DISTRIBUTION

White piedra exists both in temperate and in tropical countries, including many in South America, central Europe, and Japan, and appears only occasionally in western Europe Scott's case is the only one reported from North America. Black piedra is found only in a tropical setting, in South America, the East Indies, Java, Thailand, and Cochin China (Vietnam).

ETIOLOGY

The cause of white piedra is Trichosporon beigelii and that of the black form Piedraia hortai High humidity and abundant rainfall are apparently predisposing factors No age is exempt. Both sexes are vulnerable. The disease is said to develop in persons who swim or wash their hair in stagnant river water

CLINICAL CHARACTERISTICS

One or more nodes are securely attached to the surface of hair The discrete, firm nodules are thought to develop on hair near the scalp They

2. CULTURAL CHARACTERISTICS.—Corynebacterium tenuis (Crissey *et al.*) is a rough or smooth, compact, white, glistening, mucoid colony. Pure cultures were obtained by primary isolation using pour plates of Difco heart infusion agar and incubating at 37 C. Transfers were made on horse blood agar.

3. CULTURE MOUNT.—The organisms were gram positive but did not stain with the periodic acid-Schiff method. Some strains of this diphtheroid were almost entirely coccal and others mostly rods. There was no true branching or definite hyphae.

4. ANIMAL INOCULATION.—Mice are not susceptible.

5. DIFFERENTIAL DIAGNOSIS (LABORATORY).—When a node is prepared with KOH and examined, the delicate rods or cocci can be seen Piedra may be excluded by the absence of sturdy septate hyphae. The cultural appearance does not lend itself to differentiation from other diphtheroids. However, Crissey and his associates differentiated C. tenuis from ordinary diphtheroids, since it is not stimulated by the addition of lipids and glycerin to the medium, ferments lactose and dextrose, and grows best at an alkaline pH.

TREATMENT

The daily use of 10 per cent xylene in petrolatum sometimes dissolves the concretions Shaving the part is the fastest and surest cure. Recurrence is common. Scrupulous cleanliness is essential to prevent recurrence.

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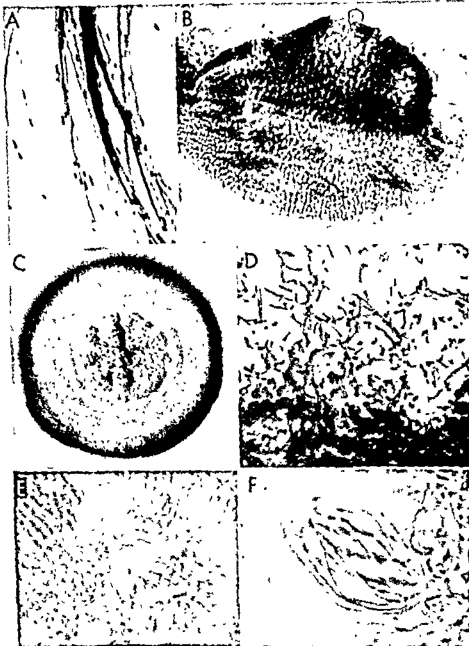


Fig 76 **Piedraia hortai, cause of black piedra** A, adherent nodes irregularly present along hairs B, black node partly surrounding hair, × 200 C, colony after six weeks on dextrose agar D, section of colony showing coarse filaments arising from core E, crushed node revealing ascus F, single ascus showing eight twisted ascospores. (*From material kindly sent by Dr F V B Dumoulin, Sumatra, Indonesia*)

gradually enlarge and become noticeable grossly only when, by normal hair growth, they are near the distal portion. As Scott pointed out, it would be easy to miss the diagnosis unless there was a contrast between the color of the hair and that of the node. Sometimes the nodes can be felt when hair is drawn through the fingers. The nodes may be either light brown (white) or black. The skin and the hair are otherwise unaffected. The scalp is the predominantly involved site, but when the beard and mustache are allowed to grow, these areas may be affected. There are no subjective symptoms.

DIFFERENTIAL DIAGNOSIS

Lepothrix can be distinguished by the color of the node, the location, the lack of fluorescence, and the microscopic appearance in KOH. Other scalp disorders must be considered, such as trichorrhexis nodosa, monilethrix, nits, trichonodosis, and artefacts. Microscopic examination is often necessary to be certain.

MYCOLOGY

1. Direct examination —In white piedra, the nodule reveals a mycelial mass, segmented irregularly, and blastospores are present. In Scott's case, these predominated. In the black variety, the hyphae are larger and have numerous septations. Numerous asci containing a few ascospores are also present.

2. Cultural characteristics —The growth of T. beigelii is cream-colored, discrete, and pasty, with surface irregularities. The colony of P. hortai is dark green to black and limited in growth, with an uneven surface.

3 Culture mount —With T. beigelii, at first only blastospores are seen, but later mycelium appears and still later chlamydospores. With P. hortai, septated mycelium and chlamydospores are shown. Simons stated that ascospores are never seen

4. Filtered ultraviolet rays —*No fluorescence is noted*

5 Differential diagnosis (laboratory) —In a KOH preparation the diameter of the filaments (2 to 4 microns) is larger than that of the organism of lepothrix, whose filaments are more threadlike The cultures of T. beigelii and P. hortai are distinguished by their color, consistency, and surface irregularity. Other fungi, such as T. verrucosum or yeastlike growths, may be considered, in which case the microscopic characteristics will differentiate them.

PROGNOSIS

There is a tendency to relapse under tropical conditions, and particularly if the bathing habits of the individual are unchanged

19. Chromoblastomycosis

(Dermatitis verrucosa)

THE chronic mycotic disorder known as chromoblastomycosis or dermatitis verrucosa is caused by one of at least three species of related atramentous fungi and is manifested by superficial papillomatous or verrucous growths.

GEOGRAPHIC DISTRIBUTION

For the few cases that have been reported, there is a remarkably wide geographic range. In the United States, the disease has been reported from Boston, Texas, North Carolina, Georgia, St. Louis, Philadelphia, Florida, Michigan, and Louisiana (nine cases). The majority of cases have been recognized in South America, Puerto Rico, Cuba, and Australia. An instance of the infection in the Dominican Republic was reported by Carrión and Pimentel-Imbert. According to Conant *et al.*, it has also been observed in Russia, Japan, and South Africa.

ETIOLOGY

According to Carrión, three fungi are recognized as causative Both he and Emmons stated the belief that there is a generic relation between them The fungi are Hormodendrum (Fonsecaea) pedrosoi, Hormodendrum (Fonsecaea) compactum, and Phialophora verrucosa. Conant and Martin also included Hormodendrum langeroni as a proved cause. According to Weidman, infection usually takes a direct route from the exterior after *injury, particularly from wood Most patients are mature men, predominantly* of the working class

CLINICAL CHARACTERISTICS

There may be a superficial resemblance to tuberculosis verrucosa cutis or to blastomycosis The lesions usually develop unilaterally on the foot or

TREATMENT

Shaving is a certain cure. Vigorous shampooing and the application of 1.2,000 solution of bichloride of mercury is useful when the former is not advisable. Xylene is an efficient remedy to detach the nodes

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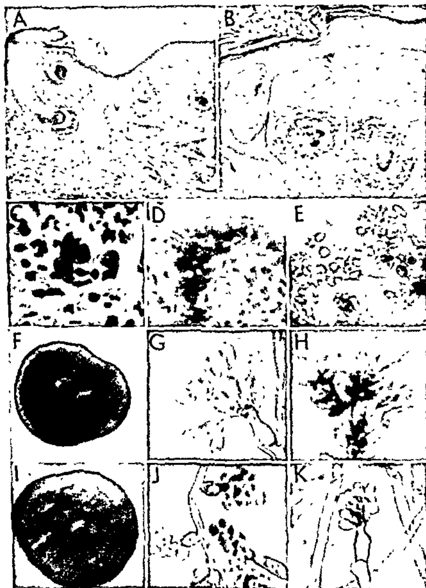


Fig 78 **Chromoblastomycosis.** A, section from superficial proliferative lesion showing pseudoepitheliomatous hyperplasia and cell clusters surrounded by inflammatory reaction, × 60 B, section from lesion of mycetoma type with
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sporulation in strain isolated from mycetoma, × 1,500

is never seen, since reproduction takes place by division. The three isolates will be described separately.

1. HORMODENDRUM (FONSECAEA), PEDROSOI.—(*a*) *Cultural characteristics.*—After four weeks the colony on dextrose agar has the shape of a low cone and a diameter of about 45 mm The margin is even. The surface is covered with a grayish nap. Zonation may appear. Thus, successively from the center to the periphery, a typical colony presents concentric zones of olive-black, brownish olive, olive-black, brownish olive, olive-black, olive-gray, and gray. The colors vary somewhat according to the underlying mycelium and the degree of sporulation. After two or three months the colonies are brown

(*b*) *Culture mount.*—A branched or unbranched conidiophore bears brownish-olive spores at the tip and, in later cultures, on the sides as well. A secondary and occasionally a tertiary spore may form from the first spore. Spores sometimes appear in branching conidial chains The spores may vary considerably in size and shape. Disjunctors, defined by Emmons and Carrión as "the narrowed end of the spore and the thickened wall which surrounds and terminates it," are usually to be found In a specimen from old cultures or in one grown on cornmeal agar, the Phialophora type of conidiophore may appear. It is bottle-shaped, being restricted where the spore is formed. Above this the wall flares, forming a cup from which conidia are extruded

(*c*) *Filtered ultraviolet radiation.*—There is no change in color, the black being more intense No fluorescence is to be noted.

(*d*) *Human inoculation* —Azulay was able to reproduce the disease by inoculating a suspension of H pedrosoi into a scarified site. A papule developed in three weeks, after five months several others had appeared. In the course of one year the lesions became warty. The pathologic appearance was that of a granuloma H pedrosoi was demonstrated and also cultured

(*e*) *Animal inoculation* —Characteristic lesions are produced in rats. Emmons and Carrión found that several saprophytic species of Hormodendrum were pathogenic for rats, with only mild lesions. Azulay could inoculate his strain into the testes of guinea pigs and white rats.

(*f*) *Differential diagnosis* —Acrotheca and Trichosporon may be readily excluded by the observation of branching chains of spores

2 HORMODENDRUM (FONSECAEA) COMPACTUM —This fungus grossly resembles H. pedrosoi on artificial media, but it grows more slowly, the surface is irregular and uneven. and the border is indented The culture mount shows H. compactum (still in comparison with H pedrosoi) to have coarser mycelium, thicker cell walls, and more pigment Branching occurs at sharper angles, and there are several other points of differentiation The appearance under filtered ultraviolet rays is similar to that noted for H pedrosoi.

3. PHIALOPHORA VERRUCOSA — (*a*) *Cultural characteristics* — The differentiation by inspection from H pedrosoi may be difficult. The

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& Syph. [illegible]

growth is greenish brown; it is covered with a short nap and has a grayish border.

(*b*) *Culture mount.*—This reveals typical flask-shaped conidiophores

(*c*) *Filtered ultraviolet rays.*—The appearance is similar to that noted for H. pedrosoi.

IMMUNOLOGY

Conant and Martin noted that the sera of rabbits immunized with H pedrosoi and H. compactum had a high titer of complement-fixing antibodies for their respective antigens and for each other. With P. verrucosa and H. langeroni, complement-fixing bodies were present only for the homologous fungus.

PROGNOSIS

While there is no tendency to spontaneous recovery, the prospect for cure in early cases is good. There is no need to fear internal involvement.

TREATMENT

The administration of potassium iodide by mouth or sodium iodide by intravenous injection has proved curative in a number of instances Calciferol, either alone or combined with potassium iodide, is recommended by Bonilla. Roentgen therapy appears to be indicated, since it is effective in disorders of somewhat similar pathologic characteristics. Conant *et al.* treated one patient with copper sulfate administered by means of iontophoresis and obtained a good result after five months. When the condition has been localized to a small area, electrodesiccation and curettage has proved successful

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Fig 79. Tinea nigra (C Werneckii). A, pigmented plaque with sharp borders in typical location (*courtesy of Prof J Ramos e Silva*) B, nummular, patchy lesions C, and D, fresh preparations of scrapings (B, C, *and* D, *courtesy of Dr Artura L. Carrión*)

20. Tinea Nigra*

TINEA nigra is a relatively rare, mostly tropical mycosis characterized clinically by the development of dark-colored macules located as a rule on the palms. It is caused by a fungus of the so-called "black yeast" group, which can easily be cultivated in the laboratory.

HISTORY AND DISTRIBUTION

Described first by Manson from southern China in 1872, the features of the disorder were well delineated in 1905 by Castellani. The first account of the disease in the Western Hemisphere was given in 1898 by Montoya y Flores, who classed it as one of the clinical forms of pinta (*Caraté noir*) found in Colombia. In 1916, G. C. Cerqueira-Pinto described the infection as observed in Brazil and named it keratomycosis nigricans palmaris.

Although not nearly as common as the other chromophytoses, tinea nigra should not be considered an extremely rare disease The reports of cases in Asia, Java, Brazil, Colombia, Central America, Cuba, Puerto Rico, and the United States are indicative of its widespread geographic distribution

ETIOLOGY

Tinea nigra has been observed at different ages from the second to the fifth decade inclusive It is reported to show no predilection for sex or race In a comparatively small series of sporadic cases in Puerto Rico, however, infections in females were predominant and the patients were all white A laboratory infection was reported by Ramos e Silva.

CLINICAL ASPECTS

The macules of tinea nigra may vary in color from black to different

* Somewhat condensed from a manuscript generously submitted by Arturo L Carrión, M D, Puerto Rico

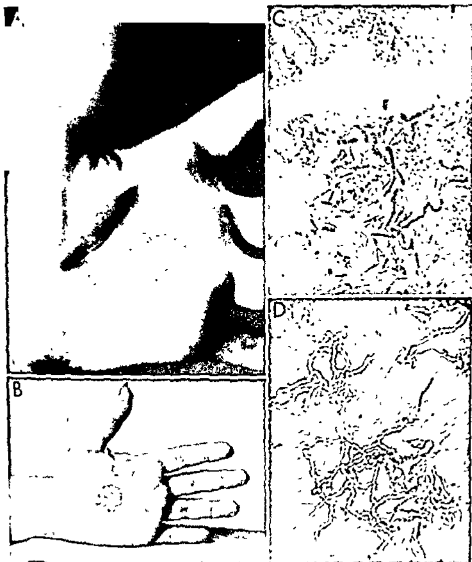


Fig 79 Tinea nigra (C. Werneckii). A, pigmented plaque with sharp borders in typical location (*courtesy of Prof J Ramos e Silva*) **B**, nummular, patchy lesions **C**, and **D**, fresh preparations of scrapings (**B**, **C**, *and* **D**, *courtesy of Dr Artura L Carrión*)

shades of gray, some of them resembling silver nitrate stains. The lesions are roundish, of various sizes, sometimes almost imperceptibly elevated, and occasionally scaly. They may be discrete or confluent, numerous or scanty. The infection is usually confined to the anterior aspects of the hand and wrist, but it may also affect other parts of the skin. There are no subjective symptoms.

DIFFERENTIAL DIAGNOSIS

The clinical picture of tinea nigra is so characteristic that it can hardly be confused with any other pathologic condition except, perhaps, a pigmented nevus or a silver nitrate stain. Scaling, when present, is a helpful sign. The more usual fungous infections of the hand, such as trichophytosis (T. mentagrophytes or T. rubrum), are inflammatory. The diagnosis may be established through laboratory examination of epidermal scrapings from the lesions, where the infecting fungus may be easily recognized.

HISTOPATHOLOGY

The fungus thrives almost saprophytically on the surface of the infected skin without producing any important tissue reaction. The epidermis appears slightly thickened, is somewhat split in places, and contains light-brown hyphae and blastospores in the superficial layers. The dermis shows few, if any, foci of lymphocytic cells.

MYCOLOGY

Tinea nigra has been associated with two supposedly different fungus species, namely Cladosporium mansoni (Castellani, 1905, Pinoy, 1912), isolated and studied in Ceylon, and Cladosporium wernecki (Parreiras-Horta, 1921), obtained from cases in Brazil When cultured under the same conditions in the laboratory, the two organisms reveal many similarities, which have led us to suspect that they are essentially identical or, *at the most, varieties of a single species*

There is a possibility that the differences between these two organisms noted at the present time may have resulted from pleomorphic changes taking place in Cladosporium mansoni, which has been kept in artificial culture in the laboratory for nearly 50 years. Unfortunately, the original description of the latter fungus does not offer a complete account of its morphology at the time of isolation, a fact which further precludes comparative studies on the basis of that description If they are finally proved to be identical, the binomial Cladosporium mansoni would have priority and Cladosporium wernecki would fall into synonymy Some of the cultural and microscopic features point to the genus Pullularia as a close relation.

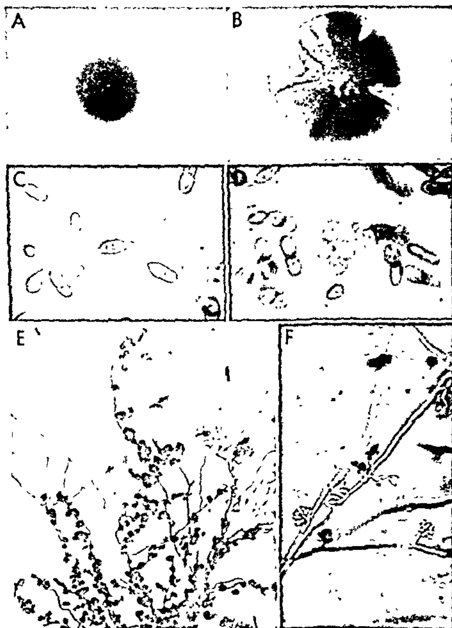


Fig 80 Tinea nigra (C. Wernecki) A, culture two weeks old on 4 per cent glucose agar
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drum type, × 430 (*Courtesy of Dr Arturo L Carrión*)

DIRECT EXAMINATION

The fungus of tinea nigra is constantly found in the scrapings from skin lesions. Fresh preparations reveal the presence of filaments and blastospores. The filaments are refractile and light olivaceous in color, 6 to 3 microns in width, engorged in places, long or short, branched, septate at irregular intervals, tortuous in course, and sometimes entangled, forming small masses which resemble nodular organs. Laterally, they have tiny conical apiculi around which blastospores are gathered in small or large groups, sometimes in mosaic arrangement. The blastospores may be fusiform, oval, spherical, or irregular in shape; they measure 4 5 to 7.5 by 2.5 to 5 microns, and many of them show budding.

CULTURAL CHARACTERISTICS: *Cladosporium wernecki*

Cultures from single spores on glucose, cornmeal, and Czapek-Dox agars show minor differences but are essentially alike. For a few days after inoculation, the growth is black, shiny, and yeastlike, but by the end of the first week, moist-looking hyphae become visible at the margin.

The culture pattern is most characteristic on glucose agar about the 14th day At this time the colonies are generally circular, approximately 15 mm. in diameter, and slightly raised in the center. They show three distinct zones At the point of inoculation there is a convex, irregular, black prominence measuring about 3 mm across and retaining its original yeastlike appearance, around this prominence there is a gently sloping, moist-looking, black, minutely granular zone about 5 mm wide, and surrounding this, is a narrow, flat, shallow margin which is moldy in appearance and brownish in color

After the second week the cultures gradually, but progressively, lose their moist character, taking on a dark greenish hue, and a considerable amount of dry aerial mycelium develops This mycelium may take two different forms, one of which is represented by outgrowths of fine, light-gray hyphae, and the other by dark-olivaceous, shallow, feltlike sectors The light-gray, moldy growth may be transplanted and reproduced indefinitely as a variant in the laboratory without reversion, while subcultures from the olivaceous sectors always revert to the original type.

For the purpose of description, three different phases of the parasite will be considered, namely a yeastlike phase, a Candida-like phase, and a moldy phase

1. Yeastlike phase —Early cultures of Cladosporium wernecki consist of masses of oval, spherical, or irregular budding cells, many of which become bicellular through the development of a septum perpendicular to the long axis. Budding takes place at one or both poles in either the monocellular or bicellular forms The newly born buds grow to a certain size, then fall off, and, when mature, continue to multiply by budding Succes-

sive buddings from the same point in the same cell have occasionally been observed, and chain formations are noted at times when daughter buds fail to separate from their mother elements, with continuation of the budding process at the distal pole.

2. CANDIDA-LIKE PHASE —This phase becomes apparent when many of the yeastlike [illegible] moist, creeping [illegible] The hyphae are [illegible] cell wall thin and light colored when young, becoming thicker and darker with age. The blastospores are born and shed off in succession, one by one, on tiny, truncated, conical prominences disposed laterally or terminally on long or short branches, and they tend to agglutinate at the point of origin to form the clusters already mentioned. Occasionally some blastospores fail to separate from the mother hyphae, and by a series of secondary buddings, they give rise to simple or branched chains, usually very short and with some of the spores bicellular, as in Cladosporium (Hormodendrum). In other rare instances several primary—not catenate—spores, arising from separate apiculi at the tip of a branch, may also fail to fall off, and in such instances the general appearance of the sporehead is suggestive of either Acrotheca or Sporotrichum.

3. MOLDY PHASE —Cultures of the gray, moldy variant reveal a profuse growth of fine, septate, branching mycelial elements, with thin, light-colored walls, and hyaline, somewhat granular protoplasm. Sporulation takes place as in the phase previously described but is scant and somewhat abnormal.

PROGNOSIS

The infection may easily be eradicated with local treatment.

TREATMENT

About any type of antifungal preparation will be successful. Tincture of iodine (U S P.) and Whitfield s ointment are commonly used and should be applied daily

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21. Rhinosporidiosis*

RHINOSPORIDIOSIS is an infection caused by the fungus Rhinosporidium seeberi, resulting in chronic, friable, papillomatous, and polypoid lesions primarily involving the mucous membranes. The commonest site is the anterior part of the nose, but lesions have also been found in the nasopharynx, larynx, palate, vulva, lips, conjunctiva, lachrymal sac, urethra, vagina, and penis and occasionally in the skin.

HISTORY

[illegible]

was named Rhinosporidium seeberi in 1900 by Wernicke. From India, O'Kinealy described his observations in 1903. In 1905, Minchin and Fantham studied the same pathologic material and named the parasite Rhinosporidium kinealyi Seeber in 1912 established the synonomy of R kinealyi and R. seeberi Several clinical papers have been published in India by Kurup, Wright, Tirumurty, Stanton, Kirckpatrik, Cherian, Allen, Mandlik, and Purandare and Deoras

ETIOLOGY

Rhinosporidiosis is caused by a microbial organism usually accepted as a single species of fungus, although attempts to prove this etiology conclusively by culture or animal inoculation methods have not been successful The name most commonly employed is Rhinosporidium seeberi

DISTRIBUTION

Although isolated cases have been described from many parts of the

* In the preparation of this chapter the collaboration of Dr Sharat C Desai, of Bombay, India, is gratefully acknowledged

world, the disease is of endemic proportion only in India and Ceylon It is particularly prevalent in the north, east, and southwest part of India.

The disease occurs more frequently in the second to the fourth decades of life, although no age is exempt. It is difficult to determine the age of onset, as the infection apparently may remain subclinical for a number of years. Males are affected 10 times as frequently as females Because of the geographic limitation of the endemic foci, the majority of cases have occurred in Asiatics, but it is apparent that no race is exempt. A large percentage of the infections occur in agriculturists. A series of cases among divers who strike their faces against the sand has been reported by Mandlik It is evident that these occupations present opportunities for exposure to the infection.

EPIDEMIOLOGY

Various modes of transmission of the infection have been postulated, but none has been proved Direct transmission from person to person seems to be precluded, since no authentic examples of multiple infections in families have been found Noronha and Mandlik expressed the opinion that the disease is spread by bathing in or diving into infected water in swimming pools or rivers Noronha reported a series of cases acquired by diving into sandy rivers. The rarity of the disease in females also suggests the water-borne mode of infection, since women in India do not frequently bathe in open places, such as pools and rivers, because of social inhibitions

Contiguous areas may be infected from a primary lesion by autoinoculation with the fingers and nails, as postulated by Forsyth, Ingram, Karunaratne, and Tirumurty, but Dhayagude and Tirumurty stated the belief that local dissemination can also occur occasionally, which would explain a few cases of generalized cutaneous lesions.

CLINICAL CHARACTERISTICS

In more than 90 per cent of the cases reported, the principal location of the infection was the nose and nasopharynx. In the nasal cavity, the vestibules of the anterior nares are the most frequently involved areas. The lesions may be single or multiple, and the majority of them are pedunculated Sessile growths arise directly from the mucosa and are in the form of small papules, nodules, or leaflike processes, which look like cauliflower when they are profuse The color is usually pink or red, interspersed with gray or white translucent dots, representing mature sporangia of the fungus. The latter characteristic may not be visible if the growth is covered by a blood clot or by mucopus Large growths are polypoid and bleed easily on being touched They look like strawberries or mulberries, owing to yellowish dots interspersed on a red fleshy growth. The pedunculated polyps may be mobile and may either protrude from the nares or extend backward into

A

B









the nasopharynx, causing obstruction of breathing when sufficiently large

The symptoms are usually attacks of rhinitis, accompanied by a blood-tinged discharge. Other common presenting symptoms are epistaxis, nasal obstruction, and a sensation as of a heavy foreign body within the nose. There may also be pain or itching

Laryngeal involvement is rare, causing hoarseness and acute attacks of dyspnea. Lesions of the palate or fauces are usually seen as sessile papillomata. Ocular rhinosporidiosis involves the conjunctiva and lachrymal sac. Granulomatous or polypoid growths are frequently seen in the fornix, suggesting acuminate condylomas in appearance. They may be entirely asymptomatic or accompanied by lachrymation and sensations as of the presence of foreign bodies These also bleed easily when touched Involvement of the lachrymal sac gives rise to a soft, fluctuating swelling visible in that region near the inner canthus Pressure upon this mass may cause blood to be extruded through the lachrymal duct.

Skin manifestations are rare, only five cases having been recorded They are of two types. (1) wartlike, papillomatous, sessile tumors in the areas contiguous to the nose and face, and (2) subcutaneous, disseminated nodules, later ulcerating and fungating on the skin The latter condition has been reported in only two cases, one observed by Allen and the other by Dhayagude, who believed it to be due to hematogenous dissemination. He could not demonstrate the organisms in the blood stream, however, nor were there signs of septicemia Nevertheless, the presence of spores in blood vessels in sections from affected tissues has been reported

Papillomatous growths in the urethra and on the penis have been recorded in two cases by Ingram and by Dhayagude There was no hematuria In appearance the growth resembled condyloma acuminatum

HISTOPATHOLOGY

The essential microscopic features of a section are papillomatous hyperplasia of the mucosa, with formation of rugae, and the presence of sporangia in various stages of development on the free border of the growth Some of these may be empty collapsed shells, indicating that the spores have been discharged If the lesion arises from the anterior nares, the finger-like processes of the papilloma are covered by stratified squamous epithelial cells, if from the posterior part of the nasal cavity, by columnar epithelium with many mucous glands

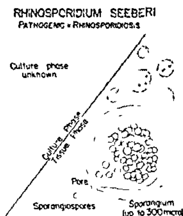
The stroma is composed of connective tissue containing inflammatory cells, spores of Rhinosporidium, many newly formed capillaries, and blood vessels There may be areas of hemorrhage from ruptured vessels. The cellular infiltrate consists principally of polymorphonuclear cells, and sometimes eosinophils, plasma cells, lymphocytes, histiocytes, and Langhan's type of giant cells The last-mentioned are frequently seen to be situated near a ruptured pore or around the sporangia

The sporangia are usually located near the free border of the epithelial lining, compressing the epithelial cells and breaching their continuity at some spots, where spores of various sizes and in various stages of development may be seen to be escaping from between the papillary processes.

MYCOLOGY

The life history of R. seeberi was originally described by Ashworth and later studied by Karunaratne. The former classified the organism among the Phycomycetes, suborder Chytridinea. The present accepted position of the organism is in the class Phycomycetes, order Chytridiales, family Coccidioidaceae.

In the early trophic phase, the organism is a well-rounded or oval cell the size of a red blood cell, 5 to 8 microns in diameter, with a clear vacuo-



lated cytoplasm enclosed in a well-defined chitinous membrane. It is found usually in the free connective tissue spaces, but occasionally it may be intracellular in a phagocyte. The spore increases in size to about 12 microns in diameter, exhibiting a doubly contoured wall, a nucleus, and cytoplasm. As the parasite grows further, the nucleus divides many times. When the cell is about 100 microns in diameter, a thick cellulose layer is deposited under the chitinous wall except at one spot, which is destined to be the future "pore" through which the spores will escape when they are fully developed. Nuclear division continues until about 4,000 nuclei are present in the sporangium. The cytoplasm also begins dividing at this stage, enveloping the free nuclei to form rounded mature spores, which further divide twice, so that about 16,000 spores may be present in a single mature sporangium, which then is white and just visible to the unaided eye, measuring about 300 to 350 microns. The wall of the ripe sporangium shows two distinct layers—the inner cellulose and the outer chitinous—except at the pore, where the cellulose layer is thinned out. The spores in

the sporangium do not all show the same maturity, fully developed spores being in the center or near the pore and immature spores at the periphery or at the pole opposite the pore. The fully mature spore contains a well-differentiated nucleus and globules of stored food material to be utilized during the further development of the spore. The spores are liberated through the pore by the rupture of the wall membrane, by differences in the surrounding pressure, or by differences in the osmotic pressure developed in the sporangium and in the surrounding tissues; each spore then begins the evolutionary cycle again.

Although the organism has been accepted as a fungus since Ashworth's studies, attempts at culture and animal inoculation have been unsuccessful. Dhayagude reported that the parasite could be maintained in a well-preserved state in Lowenstein's and potato-water media for a period of three months but showed no evidence of growth. Rettie reported positive cultures on Sabouraud's medium, but his findings have not been confirmed by other workers. Rao suggested the saprophytic existence of the fungus in animal feces and reported obtaining positive cultures on sterilized fecal matter from cows and on Sabouraud's medium containing cow-dung or horse-dung extract. Rao's work, also, has not been corroborated. Attempts at animal inoculation in dogs, guinea pigs and monkeys have been unsuccessful.

DIAGNOSIS

The diagnosis is established by the clinical character of the growth, by microscopic demonstration of spores in the nasal discharge, and by sporangia in histopathologic secti [illegible] acteristic enough for clinical [illegible] differential diagnosis one must consider all inflammatory granulomas, including syphilitic, tubercular, leishmanoid, and leprotic granulomas, rhinoscleroma, and neoplasms, such as polyposis, hemangioma, angiofibroma, sarcoma, epithelioma, and leukemid.

PROGNOSIS

In general, the evolution occupies several years and the prognosis is benign except when the growth is in the larynx or there is dissemination via the blood stream. Since it is impossible to remove all the diseased tissues, part of which may look normal, the rate of recurrence is high after surgical intervention

THERAPY

Surgical treatment is frequently necessary for immediate relief of mechanical symptoms. It is preferable to employ electrocautery to prevent



Fig 8. ... diosis (R. seeberi) A, section of papule revealing different stages of

the sporangium do not all show the same maturity, fully developed spores being in the center or near the pore and immature spores at the periphery or at the pole opposite the pore. The fully mature spore contains a well-differentiated nucleus and globules of stored food material to be utilized during the further development of the spore. The spores are liberated through the pore by the rupture of the wall membrane, by differences in the surrounding pressure, or by differences in the osmotic pressure developed in the sporangium and in the surrounding tissues; each spore then begins the evolutionary cycle again.

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DIAGNOSIS

The diagnosis is established by the clinical character of the growth, by microscopic demonstration of spores in the nasal discharge, and by sporangia in histopathologic sections The appearance of the papilloma is characteristic enough for clinical diagnosis and has already been described. In differential diagnosis one must consider all inflammatory granulomas, including syphilitic, tubercular, leishmanoid, and leprotic granulomas; rhinoscleroma, and neoplasms, such as polyposis, hemangioma, angiofibroma, sarcoma, epithelioma, and leukemid.

PROGNOSIS

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THERAPY

Surgical treatment is frequently necessary for immediate relief of mechanical symptoms It is preferable to employ electrocautery to prevent

22. Superficial Mycoses of Infrequent or Doubtful Occurrence

INFREQUENT superficial mycoses may be discussed under three headings. (1) pathogenic fungi rarely isolated in the United States, (2) saprophytic fungi which occasionally assume pathogenicity for man, and (3) controversial or poorly documented fungous infections.

A. PATHOGENIC FUNGI RARELY ISOLATED IN THE UNITED STATES

1. TRICHOPHYTON EQUINUM —This is classed as a variant of T mentagrophytes by some, but Georg expressed the belief that it is a distinct species Most of the literature is from Europe and South America It has been recognized as an important cause of tinea in race horses in eastern United States Human contacts are occasionally infected.

According to Georg, the growth on culture is rapid, is white and downy, and in two weeks shows irregular folds. There is some submergence of the growth at the periphery, and the color there is yellow-orange. The undersurface of the colony is yellow-orange, later becoming rose-red Microconidia are scanty. Georg mentioned that a characteristic is the necessity for nicotinic acid to sustain growth.

2 TRICHOPHYTON GALLINAE (ACHORION GALLINAE).—This fungus is recognized as the cause of tinea in birds, specifically the disease known as white comb or favus It is rarely seen in this country

In culture, the growth is limited, compact and downy, with a tendency to radial grooves A feature is a currant-red pigment which diffuses through the medium Microconidia and macroconidia develop, particularly with the addition of yeast extract

3 TRICHOPHYTON MEGNINI (TRICHOPHYTON ROSACEUM) —There is often confusion in distinguishing this species from T rubrum and from a saprophytic Fusarium Isolates have been reported from the beard, nails, and glabrous skin, with minimal inflammatory reaction

the implantation of spores on surrounding surfaces cut by scalpel or snare.

Chemotherapy has usually been disappointing. A few cases have been reported in which no spores could be found in the nasal discharge after instillation of drops of antimony potassium tartrate (tartar emetic) in 2 to 5 per cent concentration. Allen and Dave reported usefulness of ethylstibamine (Neostibosan) by injection in a total dose of 2 to 4 Gm. in a few cases.

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experimental rats, (3) the parasite remained viable for 37 days in such animals, (4) the reports of others indicated pathogenicity of a similar strain, and (5) the pus from which cultures were secured came from a closed lesion There is no doubt that the evidence is strongly in favor of the conclusions drawn. Weidman had previously considered Scopulariopsis as capable of causing tinea unguium. We have obtained strains of Scopulariopsis on a number of occasions, frequently in repeated scrapings from the same patient, but when nails were undoubtedly invaded by fungi, this finding was, with few exceptions, incidental Usually Scopulariopsis was present superficially and the real pathogen was found in the deeper parts of the nail. In the exceptions, repeated cultures at various depths of the nail continued to yield a species of Scopulariopsis. Partial evulsion, achieved as the result of taking specimens, has resulted in cure.

In many cases reported in the last few years, a species of Aspergillus has been considered of pathogenic titer. A critical analysis of many of the reports fails to reveal sufficient evidence to incriminate the mold as more than an incidental contaminant In a case reported by Myers and Dunn, an ulcerated granulomatous lesion had been present on the back of the hand for two years. Only a Staphylococcus was obtained on blood agar cultures. Roentgen therapy and moist boric acid packs were administered for six weeks without improvement Then cultures on Sabouraud s medium yielded an Aspergillus Cure was credited to the use of an ointment containing 1 per cent copper subacetate, although it would be more logical to assume that the roentgen rays (dosage not mentioned) administered while the diagnosis was still pyoderma were more than mildly contributory to the favorable result. This case was cited by Frank and Alton, who in turn reported in detail an extremely superficial infection said to be due to Aspergillus niger in a postoperative skin dressing, which healed overnight after an application of iodine and alcohol. They had observed two similar cases previously. It is a question whether many saprophytes under the same condition would not have produced a similar picture. Frank and Alton stated that of 375 species of Aspergillus, 57 are pathogenic and 40 are pathogenic for human beings The term pathogenic seems to be rather loosely interpreted by these authors. The reports cited could be multiplied many times; this is one reason why medical mycology has become confused Careful attention to technique in removing material for culture will usually result in the elimination of surface contaminants

C CONTROVERSIAL OR POORLY DOCUMENTED FUNGOUS INFECTIONS

1 [illegible]
EXTE [illegible]
and c [illegible]
pruritus

(a) *Etiology* —While a number of writers have described this disorder

The cultural growth is downy, develops rapidly, and forms deep radial grooves. A pale rose color develops on the undersurface of the colony, later diffusing throughout.

4. MICROSPORUM SIMIAE.—This fungus (a parasite of monkeys) was isolated by us in a single instance from the scalp of a child with tinea capitis. There was a history of contact with a monkey. The diseased hair fluoresced like hair infected by other Microspora, and the microscopic appearance also was similar. On culture the growth was fluffy and white and development was slower than that of M. canis. Radial grooves were present. The culture mount showed fuseaux and microconidia similar to those of M. canis This species may indeed be a variant of M. canis.

B. SAPROPHYTES ASSUMING PATHOGENICITY

Among saprophytes which assume pathogenicity might be placed fungi which are secondary invaders when it is difficult to determine whether their presence is more than incidental. It is our opinion that much harm has been done and the progress of medical mycology delayed because of confusion due to the numerous case reports of supposed mycoses. After a critical analysis of many of these reports, one concludes that proof was frequently insufficient. It is probably true, of course, that the difference between pathogenic and purely saprophytic existence is not great; lowered resistance of the host or development of a strain of increased virulence may account for a certain number of genuine mycotic infections. It would probably be wise, however, to be skeptical regarding claims of pathogenicity of fungi of ordinarily nonpathogenic species unless more proof of the pathogenicity is offered than mere occurrence in diseased tissue. Such tissue is suitable soil for growth and propagation of fungi which would otherwise fail to affect the normal tissues of the host The ideal procedure would be reinoculation of the living organism into healthy human tissue, but this is not often possible, nor is it desirable in every case Animal inoculation can never be as valuable a diagnostic procedure, since the susceptibility to infection is not the same even in different species of animals and is not likely to be the same in laboratory animals as in human beings. Repeated isolation of a particular species of fungus, even if it is commonly saprophytic, is likely to impress the worker unduly, and the need for further proof is not considered necessary It would be helpful if, when the diagnosis is based solely on the isolation of a fungus, the reporter would use a question mark in the title to indicate doubt as to the diagnosis.

In reporting a case of nodular and ulcera
ulariopsis brevicaulis (a saprophyte found o
matter) was isolated, Markley, Philpott, and
the microorganism was not identified either in pus or in histologic section they believed it to be the cause of the disease because (1) there was reasonable exclusion of other etiologic factors, (2) granulomas were produced in

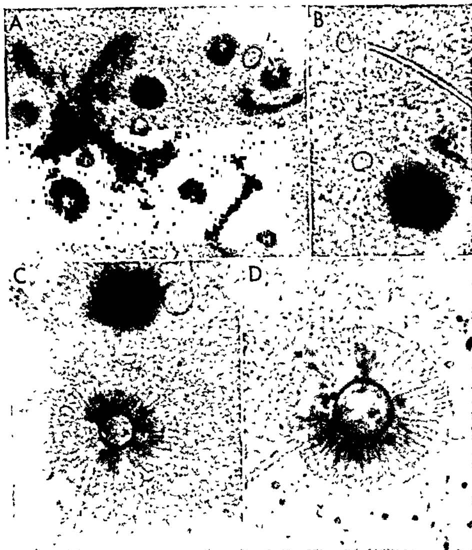


Fig 83 Aspergillus niger present in profusion in scrapings from acutely inflamed ear canal Microorganism was repeatedly cultured, and no other cause could be found for disorder **A**, numerous heads of various ages with radiating structures bearing masses of spores, × 100 **B**, young conidiophores, × 150 **C** and **D**, higher magnification showing structure of head, × 220 and × 480

as of fungous origin, few exact technical studies have been carried out. Whalen stated that species of Monilia, Aspergillus, Penicillium, and Achorion may be found He mentioned that in China and in the Americas the predominating organism is a species of Aspergillus. In the Canal Zone, however, Monilia is more often found. The question arises whether these fungi, which are for the most part common laboratory "tramps" and may be cultured from the surface of normal skin, can be incriminated as the cause of the disease in question. The evidence so far offered is not sufficient to prove beyond doubt that they can. It is possible that the special conditions present in the external aural canal, particularly with retained cerumen, also favor the proliferation of ordinary saprophytes, so that a pathogenic propensity is established. In our studies, Aspergillus has been a common finding, but autoinoculation experiments on several occasions have not been successful If a species of Aspergillus is to be considered pathogenic, it must be with the qualification that the site and the material present are predisposing factors We have cultured few fungi of recognized pathogenic titer from this site. Streptococci have also been considered as possible causative agents, since they are sometimes obtained on culture We have not noticed a common history of allergy in patients with this disorder. No age is exempt, although the majority of patients are young adults. Season and climate may have considerable adverse effect on the course of the disorder Many instances of severe involvement were observed in the South Pacific theater during World War II Swimming in infected pools has been suggested as an important factor Neurodermatitis or atopic eczema of the localized form is favored by the intense pruritus and frequent history of nervous tension Lack of family or personal history of other allergic diseases is not against this concept

(*b*) *Symptoms* —The external ear around the meatus is swollen and red A moist mass of debris is usually present and may completely fill the canal When this is removed, the affected skin is seen to be exudative. If the condition is mild or just beginning, the debris may be scanty, and at times it is dry and flaky While pruritus (worse at night) is present in almost every case, evidence of trauma is rare The disorder may extend down the canal and affect the drum It has been said that if the drum is perforated, the infection may extend to the tympanic cavity and even invade the mastoid cells The remainder of the ear may be variably involved In severe cases, the exudative inflammation may spread to contiguous areas and be indistinguishable from infectious eczematoid dermatitis

(*c*) *Differential diagnosis* —Seborrheic eczema is rarely observed in this site alone, evidence, therefore, should be sought on the scalp, behind the ears, and in other areas Itching is less troublesome in seborrhea We are unable to differentiate this condition from the exudative inflammatory disorder due to streptococci described by Mitchell as occurring on the infra-auricular fold Contact dermatitis from nail polish, hair lotion or dressing,

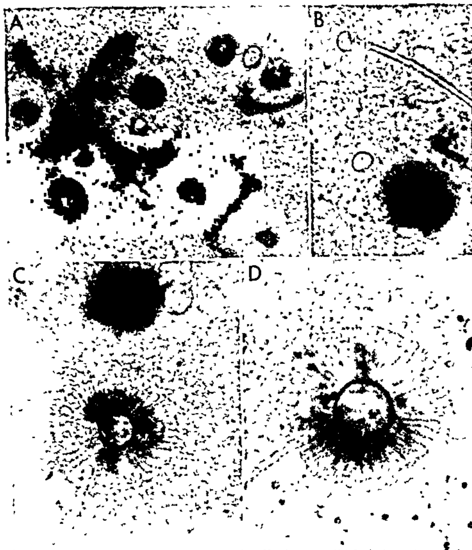


Fig. 83. Aspergillus niger present in profusion in scrapings from acutely inflamed ear canal. Microorganism was repeatedly cultured, and no other cause could be found for disorder. A, numerous heads of various ages with radiating structures bearing masses of spores, × 100. B, young conidiophores, × 150. C and D, higher magnification showing structure of head, × 220 and × 480.

or other skin-sensitizing agents is usually seen in women, is very pruritic, and often affects the eyelids.

(*d*) *Prognosis.*—There is often difficulty in achieving cure unless the disorder is treated as an eczema

(*e*) *Treatment.*—In cases of pruritus in which there are minimal objective findings, a favorable effect is usual with the following regime:

(1) No soap or water. Plug ear with cotton while bathing.

(2) A sparse amount of hydrocortisone ointment 1 per cent on an applicator applied once daily

(3) Antihistaminic drugs by mouth (*see* Chapter 25) in sufficient quantity to relieve the pruritus.

This program may be supplemented in instances of severe exudation and more extensive involvement by the application of wet boric acid compresses or at times by dilute silver nitrate solution Roentgen rays in fractional dosage are also helpful.

When there is evidence of middle ear involvement, consultation with an ear specialist should be prompt.

Irrigation and antibiotic drugs are not often required

2. SEBORRHEIC DERMATITIS (PITYROSPORUM OVALE) —During recent years many studies have been made of the possible pathogenic role of P. ovale, a fungus originally described by Malassez and also known as the bottle bacillus of Unna. The investigation of its pathogenicity has been hindered by the difficulty of obtaining a cultural growth. Success in growing the organism was reported by MacLeod and Dowling in 1928. Previously Unna, Engman, Castellani, Templeton, Acton and Panja, and Ota and Huang reported occasional success in attempts to cultivate the fungus Templeton employed a preparation containing beer wort agar Moore used wort agar (Difco), a medium made especially for the cultivation of yeasts, subcultures were usually made after three or four days Moore reported success in culturing P ovale in approximately 10 per cent of cases and attributed his failure in the remainder to a considerable concomitant growth of common air-borne fungi It was possible to inoculate other media successfully from a vigorous primary growth Benham, Emmons, and others have also been occasionally successful in obtaining a cultural growth of P ovale

In a report on the possible role of P. ovale as the cause of seborrheic dermatitis, Moore, Kile, Engman, and Engman found that inoculation of the cultures of an organism which they believed to be P ovale in human subjects and in animals frequently resulted in the development of a "dermatitis of erythema or brown scaliness," the histologic picture of which resembled that of seborrheic eczema They stated that the reproduction of a dermatitis as reported by MacLeod and Dowling was the most convincing evidence in favor of the etiologic importance of a microbe In a prior report Moore expressed doubt that the organism isolated by MacLeod and Dowling was P ovale. It seems, therefore, that rigid control tests both as to

subjects and as to the inoculated material are essential in order to determine pathogenicity by inoculation experiments. Moore, Kile, Engman, and Engman reported that cutaneous tests on 18 patients with different extracts prepared from the cultural growth of P. ovale resulted in a number of positive reactions. These reactions were manifested by the development of an area of erythema at the site of injection, and in a few instances a scaly red dermatitis appeared No mention was made of control tests. In a second and more complete study, Kile and Engman inoculated P. ovale and

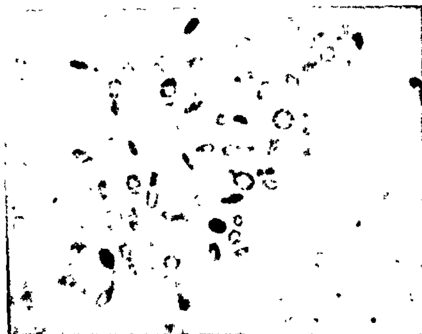


Fig 84 Pityrosporum ovale. There are variously sized cells, including dumbbell and flask-shaped cells, × 2,000

produced a scaly condition on human scalps from which P ovale was again recovered. Control tests with two other fungi failed to produce comparable inoculation results.

In a survey of the scalps of 100 patients, MacKee, Lewis, Spence, and Hopper made an arbitrary clinical differentiation into five groups based on clinical features common to each group Pityrosporum ovale was frequently noted in all groups, being present on 70 per cent of normal scalps and on 66 per cent of the scalps on which there was a concomitant skin disease In the majority of examinations, it was found that the concentration of the organism was higher on scalps with dandruff than on normal scalps. In a second series of patients it was noted that P. ovale was also a common inhabitant of the skin, more frequently found in scrapings from the sur-

face of the nose than in material manually expressed from the nose. There is still divided opinion among investigators regarding the pathogenicity of P. ovale. Many feel that the work of Engman and his collaborators is decisive and that proof of a causal relationship between P. ovale and dandruff is equal to if not greater than that of a causal relationship between M furfur and tinea versicolor.

(*a*) *Microscopic features.*—In a search for the microorganism, the chief reliance is to be placed on a direct mount. We use a technic of staining with methylene blue. The organism is noted as an ovoid or spherical cell with or without budding. The flask-shaped cell is characteristic. The diameter varies from 2 to 10 microns.

(*b*) *Cultural characteristics* —The medium which Moore found most favorable for primary isolation is wort agar, which, as already mentioned, is a Difco product with a pH of 4.8. He reported success in approximately 10 per cent of cases. The following medium may be used for subculture when it is desired to keep the growth alive:

Technical maltose, and		
Technical dextrose	aa	2 per cent
Peptone		1 per cent
Agar		1 8 per cent
Distilled water		q s.

Wheat germ oil or butter should then be added, since Benham has shown that P. ovale requires a fatty environment. We studied three strains. The growth was first noted on the fourth day after inoculation The rate of growth was slow to moderate, the ultimate size being limited. The color was tan. The cultures were compact, smooth, and glistening, with no bubbles

According to Moore, the colony measures approximately 2 cm. in diameter after 40 days. The culture is pulvinate, with radiating ridges to the periphery, a rough surface, and a few small excrescences. The color is dull and varies from light ochraceous salmon to pinkish buff.

(*c*) *Culture mount.*—The cells vary from 3 to 15 microns in diameter, *most of them being from 4 to 5 microns There are many* budding cells resembling bottles or gourds. The large cells appear to be thickly encapsulated or to have a thick gelatinous structure due to the medium. Several cells show more than one bud. The budding cells appear to be small or divided Elongated forms have had a mean length and width of 5 and 4 microns, respectively

(*d*) *Animal inoculation* —Moore's cultural growth has been inoculated into the skin of rabbits, with a resultant scaly rash which disappeared spontaneously

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23. Physiology and Nutritional Requirements of the Dermatophytes

WHEN conditions are optimal, the vegetative portion of a fungus increases and develops. If conditions are adverse, the fungus has a tendency to produce spore forms, which are more resistant. The following brief discussion presents some of the known extrinsic factors requisite for the full development of fungi.

The fungi classed as dermatophytes (which are responsible for the superficial infections) are usually found in relation to keratin, occurring in the stratum corneum, in the substance of nails, in or on hairs, or in the hair follicles. This dermatropism has been subjected to scrutiny by a number of investigators. The inability of these fungi to live or reproduce in the internal organs and tissues is remarkable. Other fungi are able to invade the deeper portions of the tissues and seldom, if ever, are found in superficial locations

TEMPERATURE

Most pathogenic fungi grow well at room temperature and more vigorously at body temperature. In the summer, fungi in culture develop more rapidly and the character of the growth is different from that of the same strain during the winter months. The counterpart in the clinical features of fungous infections is well known

MOISTURE

One of the factors thought to be important in predisposing toward fungous infection of the toes is the moisture normally present or due to lack of drying after a bath or to other conditions It is well known that in culture, growth at low humidities is slow The water requirements of fungi,

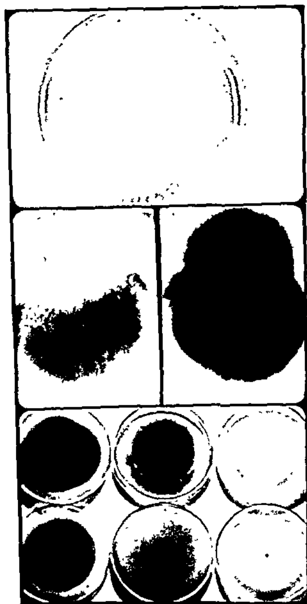


Plate II. Development of pigment at base of fungus colony growing on artificial medium.

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however, vary considerably according to the species. The normal habitat of some of the lower fungi is in the depth of a body of water. Others grow well on the surface of a liquid medium. Most pathogenic species of fungi grow best on a semisolid or solid stratum. Fungi may remain dormant for some time under natural or artificial conditions of drying, being capable of revival with the addition of moisture.

OXYGEN

With the exception of Actinomyces bovis, the common pathogenic fungi require oxygen for life and development Lacking sufficient oxygen, reproductive bodies are sparse; they may be stimulated to develop by an excess amount of oxygen.

LIGHT

In some mycoses, such as tinea versicolor, the eruption is almost invariably confined to a covered portion of the body. The fungicidal action of certain light rays has been considered as a possible explanation. In our [illegible]

action as lethal agents, although some observers have reported inhibitory action on certain fungi

NITROGEN

The manner in which the dermatophytes utilize the amino acids in keratin has been the subject of considerable speculation and some careful research. A characteristic of all keratin is its chemical stability. According to Nickerson and Williams, no enzyme has yet been found that actually hydrolyzes keratin. They believe it is possible that the dermatophytes act on keratin not through primary enzymatic digestion but secondarily by enzymatic attack on a reduction product, as shown for the clothes' moth. In culture media, the usual source of nitrogen is a peptone. All peptones are complex, containing inorganic compounds, variable amounts of amino acids, protein split products, and other substances with growth-producing capacities Mosher, Saunders, Kingery, and Williams found that T mentagrophytes would not grow on a medium containing only inorganic nitrogen Successful growth in a synthetic medium was possible only if amino acids were added Raubitschek, working with a continuous shake culture, reported that strains of T. mentagrophytes, T rubrum, and T. tonsurans showed growth on inorganic nitrogen even in the absence of carbohydrate. The carbon required for cell constituents was probably derived from the atmosphere Addition of carbohydrate caused marked increase in growth.

known vitamins and demonstrated that this is true also for T. megnini and T. gallinae. The importance of the nitrogen source in pigment production was stressed.

OTHER NUTRITIVE NEEDS

Requisite for growth or reproduction are traces of many of the minerals, such as ammonium, potassium, calcium, magnesium, zinc, iron, copper, manganese, phosphorus, and sulfur. According to Foster, the for-

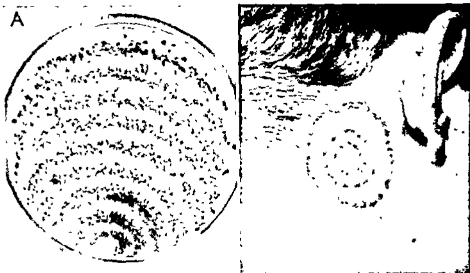


Fig 85. Comparison of variations in growth of fungi in artificial medium and on human

mation of pigment may depend to some degree on the amount and kind of available minerals, iron, copper, and manganese being particularly important This subject is considered further by Nickerson (*Biology of Pathogenic Fungi*, Chapter 10) As shown by Benham, oleic acid is a necessary ingredient of the culture medium when Pityrosporum ovale is cultivated. The hydrogen ion concentration may range between 5 and 7 In our standard dextrose agar, the pH is usually in the region of 5 6.

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With E. floccosum, no growth occurred in the presence of ammonium sulfate alone. Silva and Benham confirmed that T. rubrum and T. mentagrophytes, as well as T. gallinae, could synthesize proteins from inorganic ammonium nitrogen; T. megnini required histidine for this purpose Mosher and collaborators, as well as Robbins and Ma, determined that a suitable mixture of amino acids promoted growth better than a single amino acid. The latter authors found that the fungus could transform a single amino acid, such as asparagin, into other amino acids as necessary to synthesize its proteins. Growth is faster when a mixture of amino acids is available. Hydroxyproline is a growth inhibitor for many species of fungi. According to Nickerson and Williams, an oxidative deamination process results in the production of ammonia from amino acids; this explains the increasing alkalinity of cultures of dermatophytes.

It is of interest that a highly virulent species of fungus, such as Coccidioides immitis, is no more exacting in its nutritional demands than ordinary contaminants, such as species of Aspergillus or Penicillium. As a matter of fact, the growth factor requirements of all types of microorganisms are very similar.

CARBOHYDRATES

Goddard added various sugars to a 1 per cent aqueous solution of peptone and later measured the increase in dry weight of the inoculated fungous growth He found that T. mentagrophytes utilized dextrose, fructose, maltose, mannose, and galactose but not lactose, whereas M. canis could not assimilate lactose or galactose. In a study by Lewis and Hopper on the production of pigment by certain fungi, such as T rubrum and M. canis, it was concluded that the pigment is a metabolic product. These fungi were found to synthesize pigment in the presence of certain monosaccharides with closely related structural formulas, such as dextrose, levulose, and mannose. One disaccharide, mannitol, was useful. Pigment was not produced when the only sugars in the culture medium were galactose (a monosaccharide) and other disaccharides, triaccharides, and polysaccharides

VITAMINS

For some fungi, thiamine is a requirement for growth, Hazen reported that addition of yeast extract (thiamine content) stimulated the production of macroconidia. Raubitschek considered that a growth-promoting substance or substances may be present in yeast extract, casein digest, and peptone (Difco) Bereston noted that M. audouini had a deficiency of thiamine when casein hydrolysate was the nitrogen source Nicotinic acid was not found essential for three species of Microsporum which he studied Biotin occasionally stimulates growth Silva and Benham confirmed other reports that T rubrum and T. mentagrophytes are autotrophic for the

24. Immunology & Allergic Reactions of the Dermatophytes

DEPENDING on many factors, there exists a wide range of variation of immunity to the dermatophytes. Absolute immunity to infection is rare. A person may enjoy a relative or incidental immunity because of anatomic or physiologic factors Thus girls with long hair and adults with increased sebum or a change in the mollecular structure of the fatty acid chains are less likely to acquire a Microsporum infection. Conversely, boys with short hair and children in general, through lack of protective sebum, are more vulnerable to microsporosis. Important also is the species of infecting microorganism. M. audouini and T rubrum infections occur with a minimum of demonstrable resistance on the part of the host With these infections, as with others, there is a tendency to chronicity and efforts to cure by medicinal methods are frustrating, particularly if one expects a rapid response. In contrast, infections caused by M canis, M. gypseum, or T mentagrophytes characteristically induce inflammatory reactions, indicating considerable host resistance, and clinically the outlook for cure within a reasonable period is hopeful After recovery from fungous infections caused by the latter dermatophytes, there usually exists a resistant state in which reinfection is less likely than before. Such an immunity is usually not permanent and may afford protection only for a few weeks or at most for a few months

The nature of the immune state and the explanation for its development have been the subject of extensive studies and have excited the imagination of workers since shortly after the turn of the century In spite of evidence submitted by Marcussen and others of circulating antibodies shown by passive transfer tests, one must conclude that such a mechanism has little or no place in body defense against infection by dermatophytes. The consensus also appears to show that precipitins and complement-fixing antibodies are lacking However, Peck and Rein have recently reported a

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complement fixation test in the diagnosis of moniliasis. It will be interesting to see whether their findings are verified.

DERMATOPHYTID

The term dermatophytid denotes an eruption other than a primary infection caused by fungi or their products and due to acquired cutaneous hypersensitivity. Most instances of dermatophytid occur in patients who exhibit an inflammatory response to invasion by *M. canis*, *M. gypseum*, or *T. mentagrophytes* There is considerable variation in the appearance of these eruptions. The first report of this tissue response appeared in 1911 and was by Jadassohn, who described a follicular papular eruption, symmetric and favoring the trunk, occurring in some patients with kerion The eruption spontaneously disappeared after subsidence of the acute primary focus

Many other varieties of dermatophytid have since been described, and the reader is referred to Chapters 3 and 10, on microsporosis (*M. canis*) and trichophytosis (*T mentagrophytes*), respectively, for further details. Dermatophytid is still an overworked term. There are certain criteria which are necessary before such a diagnosis can be seriously entertained (1) There must be a culturally proved focus of infection with one of the dermatophytes. Preferably although not necessarily this could be *M canis*, *M gypseum*, or *T mentagrophytes* (2) The primary focus must be inflammatory (3) The trichophytin test must elicit a positive reaction. (4) The eruption must disappear without treatment when the primary focus is cured or becomes less inflammatory.

TRICHOPHYTIN

The chief interest in studying the problem of allergy in the superficial mycoses centers on findings from the experimental use of a fungous extract known as trochophytin derived from one dermatophyte or a mixture of dermatophytes It is not established that variation in potency results if the source is a fungus of the more allergenic type, such as *M canis* or *T. mentagrophytes* (powdery) than if *M audouini* is used

In prior editions of this text, the history and many of the experimental features were discussed in considerable detail Some of the more important facts are as follows

1 A positive reaction to trichophytin is specific and is evidence of present or prior infection by a dermatophyte It is not induced by bacteria or by other species of fungi, such as *Blastomyces dermatitidis* It cannot be elicited by repeated injections of trichophytin.

2. A positive reaction may persist for weeks, months, or years after the infection has disappeared

3. A positive reaction is necessary to complete the evidence for a diagnosis of dermatophytid

4. Occasional positive reactions are observed in adults who have no discernible fungous disease and no history of such disease.

5 A negative reaction to trichophytin does not rule out a diagnosis of a superficial fungous infection or of a prior infection, since the skin is not always sensitized. Also, the reaction to the test may change from positive

TABLE 8.—REACTION TO TRICHOPHYTIN, AFTER 48 HOURS, OF 254 PATIENTS WITH PROVED FUNGOUS INFECTION

Fungus	No of Cases	No of Negative Reactions		No of Positive Reactions			Percentage of Positive Reactions
		0	±	+	++	+++	
M canis	39	4	5	15	14	1	76
M audouini	48	18	15	8	7	0	31
T. schoenleini	10	7	1	2			20
T rubrum	50	25	13	8	2	2	24
T mentagrophytes	88	13	12	35	23	5	71
T. violaceum	6	3		2	1		50
M gypseum	4		1	1	2		75
T niveum	4	1			3		75
E floccosum	3	1	1	1			33
T tonsurans	2			1	1		100

TABLE 9.—COMPARISON OF IMMEDIATE AND DELAYED REACTIONS TO TRICHOPHYTIN FOR THREE SPECIES OF DERMATOPHYTES

Fungus	No of Cases	Positive Immediate-Negative Delayed %	Both Positive %	Negative Immediate-Positive Delayed %	Both Negative %
T rubrum	100	53	32	10	5
T mentagrophytes	150	1.5	15	72.9	10.6
E floccosum	19	15.8		26.3	57.9

to negative In children with no obvious fungous infection, a negative reaction to trichophytin is invariable A false negative reaction may occur in patients undergoing attacks of a febrile disease or receiving steroid hormones or strong doses of an antihistamine drug.

6 As a rule the more inflammatory the fungous disease, the greater the reaction to trichophytin

7 Interpretation of the test must be done with care. The test is not a substitute for a direct mount or culture

8. There are two types of reactions which may occur after an intracutaneous injection of trichophytin: an immediate wheal reaction, appearing after 10 to 15 minutes, and a delayed or tuberculin type of reaction, which is at its height in 48 hours.

9. There is no correlation between reactions to trichophytin and to Oidiomycin (an extract of Candida albicans). This is proof that Trichophyton (and Microsporum and Epidermophyton) and Candida belong to different immunologic groups of fungi, each capable of producing its independent specific hypersensitivity.

10. The location of the test site is usually the upper outer arm. However, any other part of the skin will suffice. Sometimes the skin near an active fungous infection will react somewhat more strongly than skin at a remote site; however, this is not invariable.

11. A strong reaction to trichophytin should emphasize the need for conservative methods of treatment provided the infection itself is also inflammatory.

12. If an undiagnosed, exudative or edematous, inflammatory eruption is of several weeks' duration (which would allow ample time for sensitization); if neither microscopic nor cultural studies show fungi, and if the intracutaneous test to trichophytin gives a negative result, the rash may be declared [illegible] ity of d[illegible] in the [illegible] wheal and delayed tuberculin response.

OIDIOMYCIN

A test utilizing an extract of Candida albicans is of interest but may be misleading if any reliance is placed on the result. Sensitization of the skin apparently occurs in many patients with no discernible cutaneous infection, probably owing to absorption from the gastrointestinal tract A negative reaction may occur in the presence of active candidiasis. Of 42 patients having some form of localized cutaneous candidiasis, a positive response to the test was noted in 57 per cent Of 91 patients with an infection due to a fungus other than C albicans, 45 per cent showed a positive reaction, while of 192 patients with no evidence of any type of fungous infection, 46 per cent reacted In another series of tests, C. albicans was found to be present in cultures of material from the tongue, skin, or stool of 52 of 100 patients The Oidiomycin test gave a positive reaction in 58 per cent of the patients with positive cultures and in 54 per cent of those with negative cultures, the similarity of results is noteworthy

From these findings, which substantially agree with those of other investigators, it is obvious that the test has no practical value in the diagnosis of infections due to C albicans

CONJOINT SENSITIZATION TO PENICILLIN

Clinical and experimental studies suggest that penicillin, a derived product of the mold Penicillium, contains antigenic properties similar to those elaborated in superficial fungous disease. The local application of penicillin in cases of acute fungous disease may provoke a local exacerbation Injection of the drug parenterally may result in the reactivation of a previous dermatophytid, produce in patients with present or previous active dermatophytosis a vesicular eruption of the hands and/or feet identical with the id reaction, or bring forth erythematovesicular lesions in areas of previous dermatophytosis.

Cross-sensitization experiments in the guinea pig, utilizing both skin and uterus as test tissue, disclosed an intimate relationship between sensitization to penicillin and T. mentagrophytes. Whereas the nature of this relationship is still obscure, available evidence indicates that animal tissues with an induced sensitization to penicillin have likewise developed an allergic reactivity to trichophytin.

Clinical reactions to penicillin may be classified as (1) contact dermatitis; (2) sensitization of the vascular bed, resulting in urticaria, angioneurotic edema, serum sickness-like syndrome, erythematovesicular dermatitis, erythroderma id-like reactions, and erythema nodosum (shocklike reactions are included in this group), (3) sensitization of other structures, as in asthma, (4) toxic effects, causing convulsions (especially after local cerebral application), peripheral neuritis, and possibly agranulocytosis, and (5) indirect effects, precipitating an unrelated infection by destruction of antagonistic bacterial flora.

AIR-BORNE FUNGI AS ALLERGENS

It is beyond the scope of this book to enter into a detailed discussion of air-borne fungi as allergens However, brief mention may be made of the suspected and proved role of many of the air-borne fungi, chiefly contaminants, in certain diseases classed as allerg[illegible]

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[illegible] s fail

to develop an etiologic diagnosis Further, the history and the location of the eruption may suggest the possibility that an air-borne allergen is responsible While pollens have been more logically suspected, the possibility has also been considered that fungi may act as sensitizers without causing an actual infection From this point of view we have investigated a number of cases of eczema of the hands in which the cause was obscure Patch tests with trichophytin did not reveal any consistent sensitivity either on the affected area of skin or at a site remote from the eczema. We had the same negative results when we tested with extracts of saprophytic air-borne

fungi. From a theoretic standpoint, an immediate wheal and flare response to a suspected fungous allergen given by intracutaneous injection would speak in favor of a direct relationship.

2. ASTHMA.—There have been investigations of other allergic diseases and their possible cause by the spores of air-borne fungi. Cooke found that house dust was a cause of asthma. The activity of the dust was diminished by heating. Van Leeuwen noted that in localities where patients with asthma were free of an attack there were few air-borne molds and yeasts. Cadham in 1924 reported three cases of asthma due to the spores of a wheat rust. He found positive reactions to an extract of the organism, and *acute attacks resulted from inhalation of a small quantity of the spores.* Hansen found several species of Aspergillus and Penicillium to be excitants capable of producing a paroxysm Hopkins, Benham, and Kesten reported that in a case of asthma under their observation the attacks occurred in locations in which mold spores were abundant. There was cutaneous sensitivity to a strain of Alternaria present in the patient's home, and attacks were provoked by inhalation of the extract. Feinberg, Brown, Conant, and Wagner and Rackemann pointed out the importance of molds in the patient's environment as a cause of asthma. They performed many tests with the extracts of cultured air-borne fungi, and these resulted in a high percentage of positive reactions. Wagner and Rackemann noted that many patients with asthma obtained relief when kapok was removed from their immediate environment Fresh kapok did not cause trouble, most of the reactions observed were produced by old material They found that the principle in commercial kapok active in skin tests depends on the growth of molds in the kapok (vegetable) fibers. Wagner and Rackemann also found that steam sterilization of both cotton and kapok effectively changed the materials so that molds did not grow well on them Rowe stated that all patients with possible bronchial asthma or allergic bronchitis should be tested with fungous extracts as well as with other allergens. Waldbott and Ascher considered sensitivity to rust and smut an important cause of seasonal allergy of the upper respiratory tract. In two cases they were able to reproduce asthmatic attacks by inhalation of rust They considered the development of the attack during the rust and smut season and strong reactions to their antigens to be reliable features in diagnosis

3 HAY FEVER —Instances of seasonal hay fever due to mold allergy have been recorded by Feinberg and others The evidence is suggestive and mainly based on the prevalance of air-borne spores The coincidental presence of pollens makes a sharp differentiation between the two as the probable cause, an extremely difficult problem

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25. Treatment of the Superficial Mycoses

THE MATERIAL in this chapter is intended to supplement and at times expand the specific recommendations as outlined under the various mycoses. Since 20 superficial mycoses have been discussed in detail and since treatment of some of these is similar, there would be needless duplication if the formulae and the minute details of procedure were repeated for each disease. The practitioner may have to wait a week or more before a culture verification of his clinical diagnosis is possible, but the indications for treatment at first may rest on purely clinical features, such as degree of inflammation, severity of symptoms, and location and extent of the disease process. It should again be repeated that success in management and sureness in approach to the problem of treatment rests on an accurate diagnosis, which requires clinical acumen and laboratory verification by careful microscopic and cultural study as well as other procedures, such as use of the Wood light, when hair is involved.

The problem of treating the superficial mycoses is complicated by the paucity of specifics. There are really no fungicides of merit. Drugs known as fungicides are more correctly termed fungistatic agents, and many of the reputed favorable effects may be the result of a change in the environment in which the fungus is existing Some drugs may interfere with respiration. It is fairly well substantiated that salicylic acid is effective because it is a keratolytic agent It tends to separate, swell, and macerate keratinized epithelium. The desquamative effect removes organisms present in superficial portions of the epithelium. The action of iodine is that of a protein precipitator. We are much less familiar with the mechanisms of action of other drugs. It is more than possible that mercury acts as an enzyme inhibitor, and the favorable effects from administration of sulfur, particularly noted in work with the soil fungi, have been attributed to its absorption by spores and release of H_2S, which stops germination. Sulfur is converted into sulfides in contact with proteins and alkalis The mechanical effect of X rays in removing hair may be contrasted with its usefulness as a cell

inhibitor in exudative processes. It is not to be overlooked that acidic preparations may exert a favorable influence by changing the pH of the skin surface

The chapter is divided into six sections:

A. Local medicaments, listed according to clinical indications.
B. Treatment of mucous membranes.
C. Physical agents.
D. Surgical measures.
E. Biologic and internal remedies
F. Adjunctives.

A. LOCAL MEDICATIONS

Some form of local treatment is necessary for almost every patient with a superficial mycosis. In the majority of these diseases, the only therapy required is a well-directed local attack on the infecting fungus. It is in the selection of drugs and in their incorporation into prescriptions that a [illegible]

Judgment as to when to prescribe each type of medicament comes with experience and cannot always be learned from a book. There are, nevertheless, principles underlying treatment, and, briefly, there are two of importance:

First, in fungous diseases caused by M. canis, M. gypseum, T. mentagrophytes, and others, there is a tendency for acute inflammation to develop, and with such diseases therapy must often be confined to soothing or mildly stimulating applications. In infections caused by M. audouini, T. rubrum, T. schoenleini, T. violaceum, and others, there is little tendency to sensitize the skin, and if local therapy is to be successful it must be "pushed," keratolytic and fungistatic agents being used in strong concentration With infections caused by E. floccosum, M. furfur, and others, in which the process is mildly inflammatory, an intermediate approach may be used and cure confidently expected within a few weeks.

Second, while chronic conditions ordinarily require vigorous treatment for a good response, there are exceptions. In superficial fungous diseases, the presence of subacute or acute inflammation due to secondary infection or eczematization takes precedence over signs indicating the presence of a fungus as the underlying and primary cause In such cases, the mere fact of long duration would not call for stimulating or irritating topical treatment

The available topical remedies are discussed under these headings:

1 Anti-inflammatory measures (for acute inflammations).
2. Intermediate applications (for subacute inflammations).

3. Keratolytic and fungistatic prescriptions and drugs (for chronic disorders).

1. ANTI-INFLAMMATORY MEASURES.—If the clinical signs reveal acute inflammation, one often does well to "make haste slowly."

(*a*) *Preliminary survey.*—Determine whether the inflammation is in part or wholly due to previous medication. It is usually best to stop whatever the patient is doing, since strange sensitivities occasionally develop and medicaments usually well tolerated may have an individual deleterious effect. The use of soap is interdicted. Review the clinical features for a possible error in diagnosis. Remove material for laboratory study.

(*b*) *Wet dressings or packs* (*aqueous*) —These are usually the safest and most effective, particularly if the affected skin is exudative. Wet packs should be left on for stated periods, usually one-half to one hour, and the applications repeated several times during the day, the length of the interval between dressings varying with the acuity of the condition. If there are copious exudation and severe edema, the wet dressings probably should be applied during one-half of each 24 hours. It is rarely if ever necessary to leave on a wet dressing continuously for long periods. When this is done there is a tendency for the treated part to become waterlogged It is better to leave the dressing open and not cover with an impervious material, but *this means that care should be exercised that the dressing does not dry out* during the period of application. Additional solution should be added as needed Another problem is whether the solution should be applied hot, at room temperature, or chilled. It is here that a decision in regard to the reason for the acute inflammation is important If the inflammation is primary or due to secondary infection, the use of a hot solution, kept warm by an overlying heat cradle or hot water bottle, may be considered. If there is an overtreatment reaction in the skin, the use of tepid or cold applications is preferable

The safest wet dressing is normal saline If an osmotic effect is desired, the concentration of salt should be increased Another favorite and a most useful dressing is boric acid It is customary to use this mild acidic preparation as a saturated solution (4 per cent), or one may direct the patient to dissolve one teaspoonful in an 8 ounce tumbler of hot water (boric acid being relatively insoluble in cold water). If a cold compress is required, the solution may then be chilled in ice box or freezer. Remember that boric acid is an extremely poisonous drug when ingested and should be carefully guarded against being mistaken for edible materials In cases in which these remedies are unsuitable, aluminum acetate solution (Burow's solution) diluted 1 30 may be used Benzalkonium chloride (Zephiran) diluted to a strength of 1 10,000 is well tolerated and a most acceptable application Silver nitrate (1 200 to 1 500) is a suitable remedy for localized areas of exudative inflammation and may be applied for one-half hour twice daily for a limited period (one to two days)

(*c*) *Lotions and paints* —When exudation is slight, after initial im-

provement from wet dressings, or when the inflammation is widespread, the application of a shake lotion such as neocalamine (N F.) is often useful While itching is frequently a troublesome accompaniment, it is probably best not to incorporate in the preparation any of the antipruritic drugs. Such drugs as menthol, phenol, and ethyl aminobenzoate (Anesthesin) are often effective to relieve itching, but they may also be somewhat irritating, which in the end worsens the disease and does not give any lasting effect. Itching may better be relieved by antihistamine drugs given internally. In using neocalamine lotion, care should be exercised to make sure that the lotion is applied sparingly. Not more than two applications daily are advised, as more of the medicament simply cakes on the affected skin and is often a source of irritation. An aqueous solution of starch, 6 to 10 per cent, sopped on the inflamed skin is often soothing This procedure may be repeated whenever desired. Boric solution (saturated) may also be used in this way and is well tolerated as a rule. Aqueous gentian violet, 1 per cent, has the disadvantage of leaving a stain. However, for limited use, usually on hidden sites such as the toes, it is often helpful, being a mild antibacterial agent, providing a protective coating against other irritants, and being one of the least sensitizing drugs in common use, the number of [illegible] daily. [illegible] easure lea [illegible] t time therapy A suitable powder may contribute to establishing an acid pH, and its absorptive and protective qualities assist materially in the reduction of inflammation. A powder containing boric acid 2 per cent and starch 10 per cent in talc (U S P.) is preferable to one that contains drugs, even in small quantities, which might be sensitizing to an already inflamed skin. This boric, starch, talc mixture may also be used as a prophylactic foot powder by patients who have hyperhidrosis

(*e*) *Pastes and ointments.*—These should be used with restraint, as they are not always well tolerated Particularly if there is much exudation, other medicaments are better However, for some patients zinc oxide paste (Lassar's paste) is of help even in the presence of moisture, forming a thick coating over the inflamed skin Another ointment, consisting of boric acid 2 per cent and starch 10 per cent in white petrolatum has been found useful in selected instances For lubrication purposes, a wide variety of substances are available; Crisco and Spry are vegetable greases which are almost always well tolerated and are particularly helpful for patients who have had an increase in inflammation when petrolatum, mineral oil, lanoline, and the synthetic products have been used

2 INTERMEDIATE APPLICATIONS (FOR SUBACUTE INFLAMMATIONS) — (*a*) *Wet dressings* —Occasionally wet dressings or foot baths are an important part of treatment Particularly in the vesicular lesions caused by T. mentagrophytes, boric acid soaks for one-half hour morning and night are useful Another favorite is a solution of potassium permanganate

3. Keratolytic and fungistatic prescriptions and drugs (for chronic disorders).

1. ANTI-INFLAMMATORY MEASURES.—If the clinical signs reveal acute inflammation, one often does well to "make haste slowly."

(*a*) *Preliminary survey.*—Determine whether the inflammation is in part or wholly due to previous medication. It is usually best to stop whatever the patient is doing, since strange sensitivities occasionally develop and medicaments usually well tolerated may have an individual deleterious effect. The use of soap is interdicted. Review the clinical features for a possible error in diagnosis. Remove material for laboratory study.

(*b*) *Wet dressings or packs* (*aqueous*).—These are usually the safest and most effective, particularly if the affected skin is exudative. Wet packs should be left on for stated periods, usually one-half to one hour, and the applications repeated several times during the day, the length of the interval between dressings varying with the acuity of the condition If there are copious exudation and severe edema, the wet dressings probably should be applied during one-half of each 24 hours It is rarely if ever necessary to leave on a wet dressing continuously for long periods. When this is done there is a tendency for the treated part to become waterlogged It is better to leave the dressing open and not cover with an impervious material, but this means that care should be exercised that the dressing does not dry out during the period of application. Additional solution should be added as needed Another problem is whether the solution should be applied hot, at room temperature, or chilled. It is here that a decision in regard to the reason for the acute inflammation is important If the inflammation is primary or due to secondary infection, the use of a hot solution, kept warm by an overlying heat cradle or hot water bottle, may be considered. If there is an overtreatment reaction in the skin, the use of tepid or cold applications is preferable

The safest wet dressing is normal saline If an osmotic effect is desired, the concentration of salt should be increased. Another favorite and a most useful dressing is boric acid It is customary to use this mild acidic preparation as a saturated solution (4 per cent), or one may direct the patient to dissolve one teaspoonful in an 8 ounce tumbler of hot water (boric acid being relatively insoluble in cold water) If a cold compress is required, the solution may then be chilled in ice box or freezer Remember that boric acid is an extremely poisonous drug when ingested and should be carefully guarded against being mistaken for edible materials In cases in which these remedies are unsuitable, aluminum acetate solution (Burow's solution) diluted 1 30 may be used Benzalkonium chloride (Zephiran) diluted to a strength of 1 10,000 is well tolerated and a most acceptable application Silver nitrate (1 200 to 1 500) is a suitable remedy for localized areas of exudative inflammation and may be applied for one-half hour twice daily for a limited period (one to two days)

(*c*) *Lotions and paints* —When exudation is slight, after initial im-

Salicylic acid	3 per cent
Sulfur precipitate	6 per cent
Petrolatum alba	q s.

In instances of subacutely inflamed feet or hands, in which eczematization is partially responsible, a soluble tar such as Zetar 1 per cent in Lassar's paste is often helpful.

3 KERATOLYTIC AND FUNGISTATIC PRESCRIPTIONS AND DRUGS (FOR CHRONIC DISORDERS).—These are required if one is to obtain results in treating chronic infections which reveal only slight or no visible inflammation. There is rarely any difficulty from secondary eczematization. Primary irritation should be avoided by starting treatment with a low concentration of drug, but for best effect the percentage of drug must be increased to approach the point of tolerance.

(a) *Wet dressings.*—In low grade kerionic inflammations of the scalp and beard, a wet pack *with sulfurated lime solution (Vleminckx' solution)* 3 per cent, made by adding one teaspoonful of solution to one-half tumbler (4 ounces) of hot water, may be used cautiously The first application may be left on for 15 minutes It may be repeated after 12 hours if well tolerated and more frequently thereafter according to the clinical indication.

(b) *Lotions and paints*—The fatty acids are relatively ineffectual. Asterol tincture 5 per cent may be tried Whitfield's lotion and resorcinol 6 per cent in 70 per cent alcohol are clean to use and will cause considerable exfoliation. *Castellani's carbol-fuchsin paint leaves a bright-red stain*, so that it must usually be confined to nonexposed areas. It is often surprisingly well tolerated but is best applied not more than once daily. The formula is as follows

Saturated solution of basic fuchsin	10
Aqueous solution of phenol (5 per cent)	100
Boric acid	1
Acetone	5
Resorcinol	10

(c) *Ointments*—Compound ointment of benzoic acid (Whitfield's ointment) either full strength or half strength is a standard prescription, used for years and still one of the more important remedies for T rubrum infections The original English formula is seldom prescribed at the present time *The following ingredients and percentages are customary*

Salicylic acid	6 per cent
Benzoic acid	10 per cent
Petrolatum alba	q s

White wax (cera alba) 1 to 3 per cent may be added to raise the melting point during hot weather

Asterol ointment *has also been helpful The fatty* acid products are relatively ineffectual Salicylanilide ointment 5 per cent has achieved some popularity in the treatment of tinea capitis caused by M. audouini or one

1:3,000. This solution stains the skin brown and so is not suitable for hands, but it is a good selection for subacute tinea pedis and is often used hot. One should be alert to the possibility of the development of sensitivity, which of course makes its further use undesirable. Occasionally in candidiasis of the paronychial type, a wet pack with bichloride of mercury solution 1:1,000 makes a satisfactory local application.

(*b*) *Lotions and paints.*—Aqueous gentian violet 1 per cent is always safe and is often effective, although one must bear in mind the obvious disadvantage of color when applying it in visible areas. It should be painted on not more than twice daily. The fatty acids have enjoyed some popularity and in general have the advantage that they are relatively nonirritating and nonsensitizing. Two such are propionic acid liquid (Sopronol) and undecylenic acid (Desenex). Asterol tincture (asterol) is also popular, but it has been reported as toxic when applied in the treatment of infants with tinea capitis. Pirk and Sevringhaus advised against its use in infants up to 2 years of age. The quantity of drug for children over 2 years old should be limited to 2 ounces per week and the patient watched carefully for signs suggestive of neurotoxicity. A 10 per cent solution of sodium thiosulfate is used chiefly in the treatment of tinea versicolor. Sometimes a mildly keratolytic preparation is good, particularly when painted once daily on the interdigital webs of the feet and sides of the toes. There are two such preparations: acid salicylic 2 per cent in 70 per cent alcohol and resorcinol 2 per cent in 70 per cent alcohol. These prescriptions should not be applied to the dorsal aspects of the feet or hands.

Tincture of iodine has been popular for generations as treatment for tinea corporis. The usual strength (7.5 per cent) will irritate after several repetitions. However, if it is used in a strength of 1 per cent, its daily application is possible without any difficulty.

Castellani's paint is indicated only in stubborn cases of long duration, when simpler remedies have not sufficed. One application a day is the maximum.

(*c*) *Powders*.—The boric and starch powder previously mentioned is useful as a morning application to the feet if the patient must continue to be ambulatory. Preparations containing fatty acids include undecylenic acid (Desenex, Timofax) and propionic acid (Sopronol). Asterol powder (asterol) is also available

(*d*) *Pastes and ointments*.—The unsaturated fatty acids probably are most effective in the subacute infections and are best when incorporated in an ointment base. Some of the popular proprietaries are undecylenic acid ointment (Desenex, Timofax) and propionic acid ointment (Sopronol). They are relatively nonirritating. Other remedies include ammoniated mercury 2 to 5 per cent, sulfur precipitate 2 to 5 per cent, and salicylic acid 2 to 5 per cent Mercury and sulfur are not compatible, but salicylic acid is often combined with either mercury or sulfur. A particularly useful prescription for E. floccosum infection of the groin is

training is part of the preparation which present day dermatologists undergo before they take their "Boards." One can never afford to be careless with the administration of X rays The reader is urged to become familiar with the techniques involved and to follow the precepts mentioned above and, particularly, in books devoted to the subject, such as *X-rays and Radium in the Treatment of Diseases of the Skin*, written by MacKee and Cipollaro. In fractional treatment the dose is usually in the range of 75 to 90 r once weekly for three or four weeks.

2. ULTRAVIOLET RAYS —These are of distinctly limited use in this field There are occasional situations, such as the sequelae of tinea versicolor, in which it may be desirable to administer ultraviolet rays to assist pigmentation. If a desquamative effect is desired, the "cold quartz" is preferable to the "hot quartz."

3. OTHER MODALITIES.—Another method of inducing a reaction in a limited site either for the inflammation itself or for the peeling resulting from it is to apply solid carbon dioxide slush made by dissolving powdered CO_2 in acetone Ethyl chloride spray is much less effective.

Electrolysis is occasionally useful in tinea capitis to epilate stubs of hair of limited number which have remained after cure of the major part of the disease. This requires a co-operative patient, not always to be found at the ages involved.

D. SURGICAL MEASURES

Removal of material for diagnostic purposes involves special techniques, but these are usually simple. Removal of a biopsy specimen is not often required and when indicated the procedure is similar to that employed with other dermatoses

Incision and drainage or aspiration for therapy is rarely required. One of the frequent mistakes is to incise into a kerion as for a pyogenic abscess Such treatment is contraindicated. The same error is not infrequently made in the case of a paronychia caused by C albicans

Electrosurgery and curettage or surgical excision of small areas of infected tissue is important in the early stages of chromoblastomycosis

Shaving might be described as a valuable surgical measure in treating hair infections such as tinea nodosa and lepothrix.

Manual epilation is often required to remove the few remaining hairs after roentgen epilation and is desirable in all cases of tinea capitis in which local therapy is being tried This procedure is best performed while the site is observed in filtered ultraviolet rays. Such a procedure may assist materially in early cure in kerion

TECHNIC OF SURGICAL EVULSION OF A NAIL —This is not a difficult procedure and may be performed in a properly equipped office. After sterilization of the overlying and surrounding skin of the digit with benzalkonium (Zephiran) solution, the paronychial tissue is infiltrated with procaine

of the other stubborn organisms. Reducing agents utilizing tar (2 to 10 per cent), anthralin (0.1 to 2 per cent), and chrysarobin (1 to 5 per cent) are occasionally useful. One of the latter two drugs is sometimes incorporated in Whitfield's ointment. A modification of Dreuw's ointment according to the following formula is sometimes effective when other remedies fail Since it is often irritating to the skin, its effect should be carefully watched.

Rectified oil of birch tar		6 per cent
Chrysarobin		4 per cent
Salicylic acid		6 per cent
Soft soap and wool fat	aa	42 per cent

B. TREATMENT OF MUCOUS MEMBRANES

Moniliasis of the oral cavity (thrush) as seen in babies and vaginal involvement in pregnant or elderly women are the chief problems. There are several remedies to be preferred over drugs which might be absorbed and would therefore be dangerous.

Lugol's solution diluted one-half with water is a nonirritating application which may be applied twice daily.

Aqueous gentian violet 1 per cent is also well tolerated and effective but is messy

Nystatin (*Mycostatin*) powder may be suspended in water and applied locally to the oral mucosa. Tablets for vaginal insertion are also available

C. PHYSICAL AGENTS

There are only a few indications for any form of physical therapy

1 Roentgen rays —These are useful in three distinct ways In the majority of cases of noninflammatory tinea capitis, temporary depilation of hair by administration of X rays is the best treatment presently available, the rays are also occasionally used in tinea barbae. The second indication for roentgen therapy is an inflammatory expression which either is primary or is accompanied by secondary infection or eczematization. In such cases, the administration of X rays in fractional dosage is helpful in the effect produced on the inflammatory exudate and in reducing activity of cells in the affected tissue In a third situation, namely, early lesions of chromoblastomycosis, a semi-intensive technic should be used.

It cannot be too strongly emphasized that X-ray therapy may be misdirected into a potent source of harm to the patient This is true with almost any good remedy and is a poor reason for neglecting treatment which will induce cure or hasten recovery *It does mean, though, that* a physician should not buy an X-ray machine and start using it with the thought that he can learn by himself or through reading all the intricacies and pitfalls of this modality The techniques are exact and can be mastered only through personal instruction and careful supervision. Such practical

2 Trichophytin.—The use of trichophytin in the treatment of fungous eruptions (particularly dermatophytids) has been the subject of much investigation and subsequent discussion Early reports (such as those of Van Dyck and others) were extremely optimistic. Sulzberger and Wise expressed enthusiastic belief that a new and useful method of curing recalcitrant lesions had been brought forward. They reported cases in which cutaneous allergy to species of Trichophyton had been relieved by desensitization. Subsequent investigation has produced sharply divided opinions, ranging from that of Traub and Tolmach, who expressed doubt that trichophytin is of any therapeutic value, to that of Robinson and Grauer, who obtained spectacular results with autogenous vaccines. Sulzberger later expressed belief in the soundness of the principle of desensitization but admitted that the clinical response to treatment was poor. Combes and some others have held that the principle of desensitization is wrong, as a reduction in the immune forces may follow reduction in sensitivity. It would seem that in most cases of actual fungous infection, an increase in sensitivity is desirable (provided this is linked up with acceleration of the immune forces). Thus, in infections due to T. rubrum, the lack of reaction at the site of the trichophytin test after 48 hours is too frequent to be ignored as an explanation for the chronicity of this type of fungous disease. In dermatophytid, the condition should respond when the residual focus is eliminated. We believe that the diagnosis of dermatophytid still is made too often and that this reaction is relatively infrequent The vesicular eruptions on the hands can be proved to be of mycotic origin in not more than one case in 10. In the cases in which theoretically trichophytin should be

due to any dermatophyte and in any site, including the scalp It is of interest and should be recorded that others believe trichophytin administered in small doses at regular intervals is of definite assistance in the management of recalcitrant mycoses It is their belief that it acts to stimulate resistance through production of antibodies or otherwise

3. Potassium iodide —The favorable effects from the administration of potassium iodide in sporotrichosis, actinomycosis, and blastomycosis naturally suggested that this drug might be helpful in other mycoses, including the superficial types It has been found useful in chromoblastomycosis There are three other situations in which small doses of potassium iodide may help The first is a recalcitrant, inflammatory mycosis, such as an overtreated infection due to T mentagrophytes, the second, candidiasis, and the third, mycotic folliculitis and granuloma It is usual when prescribing potassium iodide to specify the saturated solution, with the dose starting at not over 5 drops three times daily in water after meals and gradually increasing to the point of tolerance.

4 Stilbamidine —The moderate success achieved from the use of

hydrochloride. The free border of the nail is grasped with a pair of forceps, and by blunt dissection the nail is progressively separated from its bed. Care should be taken not to break up the friable nail and, when the lunula is reached, not to destroy or injure the nail bed, since this would prevent or interfere with the return of a normal nail. The last attachment of the nail should be separated by being torn gently across. With a dermal curette, special search should be made for remnants of nail which may have become detached, particularly in the lateral sulci under the nail fold. Sterile gauze is applied with pressure until all bleeding is arrested. This usually takes from 10 to 15 minutes. The region is then painted with a 1 per cent aqueous solution of gentian violet, and a loose dry gauze or absorbable gelatin sponge (Gelfoam) dressing is applied. Since exudation may be expected, the dressing should be changed in two hours. After this a daily change of dressing is usually sufficient Gentian violet should be applied each time the dressing is changed, for five or six days, after which the dressing is usually omitted We do not advise the use of an ointment after the evulsion, particularly while exudation is still to be noted.

E. BIOLOGIC AND INTERNAL REMEDIES

1. ANTIBIOTICS —The hope for an effective antibiotic against pathogenic fungi is still unrealized However, there is a possibility that such a remedy will be developed or that specifics will be found against the more stubborn mycoses In 1928, Weidman and Chambers noted that some interdigital webs were free from fungous disease, and they were often able to isolate Bacillus subtilis from such sites. Subsequent implantation of the cultural growth of B subtilis on the sites of interdigital fungous infection was followed by clinical improvement In studies along the same line we noted the rapid overgrowth of many culture tubes by some of the common molds In 1944 Lewis, Hopper, and Schultz isolated a bacterial filtrate with a potent fungistatic activity. This filtrate of Bacillus (subtilis) XG gave promise of clinical value in the treatment of the superficial mycoses However, its use was not practical, as it was impossible to remove a hemolytic component From the reports of Tolmach and Lowenthal, Hopkins and his co-workers, Schwartz, and others, several other promising isolates have been developed, but for one reason or another they have not proved clinically useful An antibiotic agent, nystatin (Mycostatin), was developed and publicized by Squibb as effective against infections caused by C. albicans It may be administered orally, rectally, in the vagina, and locally It is poorly absorbed from the gastrointestinal tract In practice, nystatin has not lived up to its early promise It is just another remedy that seems to help some patients and certainly should not be withheld in obstinate cases of moniliasis, particularly the systemic forms In the strictly local invasion of one or two sites, nystatin would appear to be no more effective than and usually inferior to other available remedies

pyoderma spreads, or if lymphangitis or other clinical signs indicate that a threatening situation has developed, some form of internal antibacterial medication is required. If possible, penicillin should not be prescribed, as it may cause a focal flare in the fungous disease. Sulfonamide therapy with sulfisoxazole (Gantrisin) 0.5 Gm. three times a day after meals is useful. Tetracyclene or one of the related compounds is preferred by many. The dose of these is 250 mg. every four hours for the first two days. The dose may then be halved for the remainder of treatment. The drug should always be taken with food, to guard against gastric irritation.

4. Antieczematous remedies.—These have been discussed in part as among the local measures available for acute inflammatory mycoses. However, in patients who become intolerant of antifungal treatment and develop a frank dermatitis, one may have to abandon all thoughts of treating the mycosis and institute treatment for an eczematous eruption. Wet dressings may not be well tolerated and are often best omitted. Soap is usually interdicted. A shake lotion or a simple ointment may be prescribed. X-ray therapy should be considered. Antihistamine drugs will provide some symptomatic relief.

this potent chemical in treating blastomycosis has led to its trial in other mycoses. Limited trials in T. rubrum infection have not been promising, although they have by no means eliminated from possible clinical usefulness one of the many related compounds.

5. Diiodohydroxyquin (Diodoquin).—The only indication for this drug is the form of moniliasis known also as acrodermatitis enteropathica. A gradually ascending dose should be administered with the aim of reaching 600 mg. four times daily.

F. ADJUNCTIVES

1. Soap substitute.—In all instances of inflammatory fungous disease, it is usual to advise against the use of soap. The reason for this is twofold: Soap is frequently irritating, and it helps to alkalinize the skin further, leaving it more vulnerable to bacteria and fungi. When it is desirable to clean the skin, such agents as mineral oil or oatmeal water may suffice. When the disorder is subacutely or mildly inflammatory, one of the available soap substitutes may be utilized. Phisoderm is acceptable, although, being in liquid form, it is not so easy to use as products in cake form, such as Dermolate and Lowila.

2. Antipruritics.—Itching, burning, and pain are not uncommonly experienced by patients with superficial fungous disease. Itching is the most usual. Sometimes the annoyance is sufficient to require special attention. In such cases one of the antihistamine drugs should be prescribed. There is a wide choice. If the patient reacts unfavorably to one drug, this may be quickly discarded in favor of another. While side reactions are common, there is little likelihood that any serious one will develop. One should warn the patient to report any untoward development, the chief being dry mouth, tingling fingers, sedation, insomnia, nausea, constipation, and dizziness. Antihistamine drugs such as diphenhydramine (Benadryl), 50 mg., and promethazine (Phenergan), 2.5 mg., almost always cause drowsiness and in consequence are often prescribed to be taken at bed-time. Thephorin, 25 mg., has the opposite effect and may therefore be taken early in the day. Pyrilamine (Neo-Antergan) 25 mg., chlorothen (Tagathen) 25 mg., and chlorpheniramine (Chlor-Trimeton) 4 mg. are often helpful if taken three times daily after meals and rarely cause any discomfort. The use of antihistamines locally is not advised.

3. Antibacterials.—Secondary pyogenic infection is a complicating problem common in T. mentagrophytes infections but less so in most other mycoses. In kerion due to any species, there is at least some element of bacterial invasion. It is sometimes practical to prescribe local therapy which will be useful for treatment of a bacterial disorder as well as for the fungous disease. Wet dressings, paints such as gentian violet, and ammoniated mercury ointment are examples. If the bacterial component requires more particular attention, neomycin or bacitracin ointment may be tried. If the

chemicals and antibiotics. New examples of such processes appear regularly. It would indeed be unfortunate if immunologic research were to be abandoned in this interim.

Each of the systemic mycoses exhibits one or more typical syndromes, which differ from each other so much that at first glance they seem related solely because of their fungal origin. However, there are some similarities, particularly some of recent discovery, which appear to be of even greater importance and which when fully understood may well furnish valuable clues to the study of immunologic processes. In this regard, coccidioidomycosis has, perhaps, the most to offer, it has already served to blaze several interesting pathways. It is almost as protean in its manifestations as tuberculosis, yet it appears to behave immunologically in a much more easily understood manner. It also possesses a unique battery of testing procedures which seem able to be correlated into such study.

In the following chapters these systemic fungous infections will be described as fully as possible in the allotted space A bibliography rather more extensive than usual has been appended to each chapter in the hope that interest in wider reading in this important field may be stimulated.

26. Introduction to the Systemic (Deep) Mycoses

SOME ten clinical syndromes are known today to be caused by pathogenic fungi which are capable of invading the human body more deeply than the skin The first of these, actinomycosis, was discovered in 1877 and was then considered (and still is by many) to be classifiable as an odd bacterial infection. The remainder, however, are indubitably caused by true fungi, and it is a remarkable fact that they all were delineated in the period between 1892 and 1908. For a long time they were so infrequently diagnosed that they attracted little attention, but in the last two decades it has become ever more evident that some of them, at least, are extremely common rather than rare and are responsible for a great deal of heretofore unexplainable human illness It appears likely that there is still much to be anticipated in this direction.

The tremendous impact of recent improvements in the treatment of other infectious diseases by chemicals and antibiotics has been felt only to a slight degree in the field of fungous disorders, where it must still be admitted that no ideally effective method has as yet been discovered. As other microbial infections are brought under control, it is inevitable that serious fungous diseases must increase in statistical incidence It is also distinctly possible that some of these infections are gradually extending their original areas of endemicity

The truly great fatal microbial scourges of mankind have been nonfungal in nature, since there is as yet no fungous infection which has caused fatalities in epidemic proportions In spite of the tremendous effort which has been spent in the past in studying immunology, this phase of many serious bacterial, spirochetal, viral, and protozoan microbial diseases is still not sufficiently well understood to furnish any practical method of defense In fact, the recent chemical and antibiotic victories in these fields have lulled us into a degree of complacence which the future may well cause us to deplore It is certainly not beyond the realm of possibility that strains of these organisms may eventually evolve which can resist all man-made

DISTRIBUTION

Actinomycosis occurs in all parts of the world—as Cope so aptly stated, "wherever there is a microscope and a laboratory" to ascertain the diagnosis. Of all the deep mycoses it is the most frequently encountered. No age is exempt, but the incidence is higher in the third and fourth decades of life. Two-thirds of those affected are males.

EPIDEMIOLOGY

A. bovis has been isolated from normal mouths and throats, it probably is usually present in these locations and in the gastrointestinal tract of most healthy human beings and animals. Examining surgically removed tonsils, Emmons found this organism in granules obtained from the crypts in 47 per cent of the cases and obtained definitive cultures in half of these. Rosebury demonstrated the organism in carious teeth and in the tartarous deposits around extracted abscessed teeth. When such an organism, usually existing as a harmless saprophyte, succeeds in causing disease, the infection is said to be endogenously acquired, Staphylococci and Streptococci are more familiar examples It is extremely important to study the contributory factors by which such usually innocuous organisms become endowed with pathogenic powers, because measures directed toward the control of such factors may be more effective therapeutically than those antagonistic to the microbes themselves In actinomycosis, trauma, which presents the fungus with devitalized tissue far enough from the surface of the body to furnish the necessary anaerobicity, is the most important of these factors; thus, the onset of the disease frequently follows the extraction of infected teeth, fractures (especially of the jaws), and bites or other injuries inflicted by the teeth of human beings or animals Disease due to other causes may serve in a similar manner by lowering tissue resistance to Actinomyces. Another important factor, and one of great significance when therapy is considered, is that a symbiotic alliance seems to be established between A bovis and endogenous bacteria, the combination exhibiting a degree of pathogenicity not possessed by either ally alone It is significant in this regard that actinomycosis is never completely reproduced in animals experimentally inoculated with A bovis in the absence of trauma or concomitant bacterial infection These facts explain the universal distribution of actinomycosis of the anaerobic type, since wherever man exists he carries with him endogenous organisms capable of producing the disease when the proper opportunity is offered It was previously thought that the habit of chewing on blades of grass or straw explained the high incidence of the disease in agricultural workers, mostly males, it is more likely that this incidence is accounted for by their poorer oral and dental hygiene and their more frequent exposure to trauma

The similarly wide distribution of the disease when caused by the

27. Actinomycosis Including Nocardiosis & Maduromycosis (Mycetoma)

THE actinomycetes, a large group of primitive fungi closely allied to bacteria, contains a few species pathogenic to man and animals. They cause actinomycosis, a chronic granulomatous suppurative disease characterized by intense induration followed by the evolution of deep abscesses, which eventually rupture and leave persistent multiple-draining sinuses In addition to this typical picture, actinomycosis is capable of such wide variations in its pathogenicity that it cannot be ignored in differential diagnosis by any practitioner of medicine, even in the narrower specialties.

HISTORY

Bollinger first delineated the disease called "lumpy jaw" in cattle in 1877, in the same year, Ponfick pointed out its similarity to the infection which Israel had recently observed in man The appearance of the tiny masses of the fungi in pus and tissues led Harz to name the organism Actinomyces ("the ray fungus") Wolff and Israel carefully studied the organism and succeeded in culturing it in 1891 The aerobic types known as Nocardiae began to be recognized in 1896.

ETIOLOGY

Actinomycosis most frequently results from infection by a single species of fungus, Actinomyces bovis, the only pathogenic fungus which prefers to grow anaerobically Certain other forms, closely allied morphologically but differing by growing only aerobically, are capable of causing the identical clinical disease, these were formerly included within the genus Actinomyces but are now usually accorded a separate generic name, Nocardia.

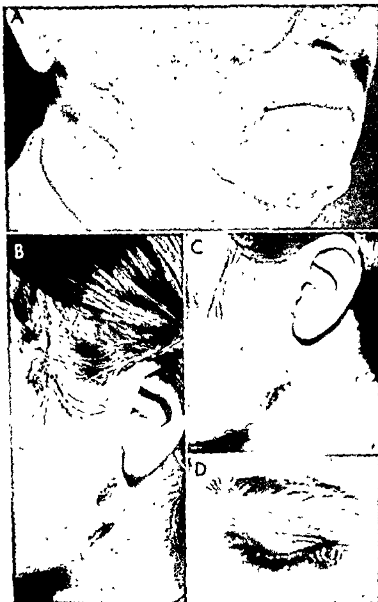


Fig 86. Actinomycosis. A, infection which, beginning in region of parotid gland, burrowed under skin to affect large portion of right cheek Some of scars are result of variola thus patient also had laryngeal carcinoma, which was apparently cured by

aerobic Nocardiae must be explained differently, since these organisms have not been found in healthy persons. Pathogenic strains have, however, been recovered from the soil, where they are apparently widely distributed along with multitudinous species of the ubiquitous soil fungi belonging to the genus Streptomyces, which they closely resemble. It is significant that in the majority of instances infection with these organisms has involved the lungs, having been caused by inhalation of dust, or the feet, because of direct inoculation of soil into wounds. Here, also, it is necessary to emphasize the importance of associated trauma or bacterial infection in conferring pathogenicity only occasionally on organisms so frequently encountered; otherwise the disease would be much more common.

Little is known of the epidemiology of the disease caused by fungi other than A. bovis or the Nocardiae. It is probably very similar to the latter

CLINICAL CHARACTERISTICS

Actinomycosis occurs in several well-defined clinical forms In over half of the cases, the involvement occurs in the region of the face or neck and is termed the "cervicofacial" type. The abdomen is the site in about 20 per cent and the chest in 15 per cent. In the small remainder of instances the disease selects other portions of the body, such as the extremities, skin, bones, joints, kidneys, ovaries, liver, or central nervous system, frequently, however, it is evident that the lesions have arisen by dissemination from a focus of one of the three commoner types

1 CERVICOFACIAL ACTINOMYCOSIS —It is fortunate that this, the commonest form of the disease, has the best prognosis. The portal of entry is the mucous membrane of the mouth or pharynx, the tonsils, or the region around the gums and teeth The infection frequently follows dental extractions and fractures or other injuries sustained in this area by persons maintaining generally poor oral hygiene or possessing carious, pyorrheal teeth The mandibular area is most often involved, usually near the angle of the jaw The maxilla may become infected directly or by way of its sinus. The salivary or lachrymal glands, the orbit, the tongue, the lower pharynx, or the larynx may be the primary site of the invasion

After a short time during which the infection reveals no special differentiating features, the overlying skin assumes a dark red or cyanotic hue, and induration develops of such firmness as to have inspired the term "ligneous (woody) phlegmon," causing marked limitation of motion and muscular spasm in the vicinity The surface becomes irregular, abscesses develop slowly and periodically and finally rupture or are incised, leaving sinus tracts which persist for months, draining serosanguineous, purulent fluid This exudate may contain tiny, yellowish, friable masses of the fungi, called "sulfur granules," to be described later in detail Healing occurs only very slowly by cicatrization Usually lesions in all these stages are present

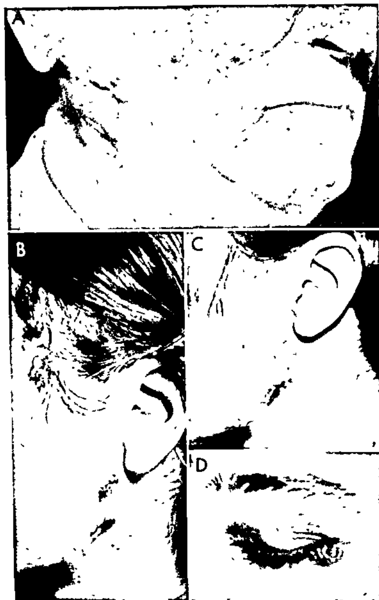


Fig 86. **Actinomycosis.** A, infection which, beginning in region of parotid gland, burrowed under skin to affect large portion of right cheek Some of scars are result of variola, this patient also had laryngeal carcinoma, which was apparently cured by [illegible]

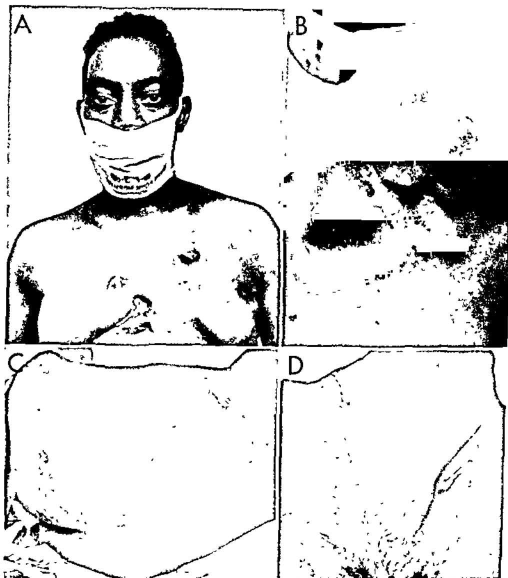


Fig 88 Actinomycosis Sinus tracts leading to visceral lesions A and *B*, *pleural and* subcutaneous sinus tracts C and D, patient from Afganistan with intestinal fistulas in pus from which granules were readily demonstrated Both patients responded well to therapy with penicillin and sulfonamides




C


B


D


E

the lungs to be involved rather than the apices Dysphagia may indicate extension to the mediastinum.

X rays may reveal massive areas of consolidation, more commonly at the bases of the lungs than at the apices and usually bilateral; such consolidations extending outward from the hilum may simulate neoplasm. A valuable differential feature in this regard is the observation within the consolidated masses of small areas of rarefaction, caused by abscess formation. Pleural adhesions are commonly observed, together with accumulation of fluid. Invasion of the ribs occurs frequently, the lesions adhering to the type of bone involvement previously described.

4. MADUROMYCOSIS, MYCETOMA, OR MADURA FOOT.—These terms have been applied to chronic, deep infections of the extremities caused by a wide variety of fungi. The disease in general conforms to the previous description of classic actinomycosis and in North America is usually identical, being caused by the same two genera of fungi, Actinomyces and Nocardia

The infection occurs at all ages, but rarely before puberty. It is commoner in persons who work barefooted in the fields and is probably usually acquired by way of an abrasion or puncture wound. Subcutaneous swelling develops, extending to produce massive firm induration in which abscesses form slowly and periodically, become fluctuant, rupture, and leave chronic sinuses draining pus and bloody fluid This fluid may or may not contain granules, which, when due to fungi other than Actinomyces, may be of various colors—white, yellow, red, or black; the typical yellowish clumps of A bovis are the commonest.

The disease may last as long as 30 years (Crocker), incapacitating the patient in from three to seven years. The limb may become enlarged to four or five times its normal size. Constitutional symptoms are usually slight, and the disease as a rule remains localized to the involved extremity.

5 OTHER FORMS OF ACTINOMYCOSIS —Actinomycosis may produce a wide variety of signs and symptoms by invading almost any part of the body, either by direct extension or by hematogenous dissemination Carrión and Cope have discussed these features in more detail than is appropriate here

Aside from maduromycosis of the foot, infection of the skin by primary inoculation is rare, Merian accepted only 25 cases as having originated in this manner When it does occur, ulcerations form and the infection gradually penetrates more deeply, eventually assuming the typical picture of actinomycosis The skin is very commonly involved secondarily, however, becoming directly infected around draining sinuses, resulting in granulomatous areas with irregular borders

Jacobson assembled 13 cases of involvement of the kidney which were thought to have been of the primary type, the remainder were considered as secondary to involvement elsewhere Cerebrospinal invasion occurs, probably always secondarily, the symptoms may suggest either infection or neoplasm Smith has reported 15 cases of ocular actinomycosis



Fig 90 Mycetoma A, early case with no surrounding edema B, advanced case with many sinus tracts and minimal tissue reaction C, early involvement associated with considerable swelling of digit D, infection of long standing with considerable deformity of foot E and F, black grain infection of hand of seven years' duration with minimal inflammatory reaction but considerable deformity Causative fungus was Fonsecaea pedrosoi (A, B, *and* C, *courtesy of Drs C F Lehmann and J L Piphin, San Antonio, Texas*, D, *courtesy of Dr Tancredo A Furtado*)

PATHOLOGY

1. GROSS PATHOLOGY.—Grossly, dense cellular infiltration, abscess softening, suppuration, sinus formation, and healing by cicatrization are all characteristic stages of actinomycotic lesions; all of these processes are usually seen simultaneously. According to the stage, the cellular infiltrate varies from an acute suppurative reaction, composed principally of polymorphonuclear leukocytes, to a granulomatous reaction containing plasma cells, epithelioid cells, and giant cells. The infection spreads contiguously by burrowing along fascial planes, and there is much intercommunication among the residual sinus tracts. Cavities filled with purulent debris are typical.

2. HISTOPATHOLOGY.—The typical microscopic picture is that of an abscess, in which the large (up to 25 microns) actinomycotic granule is usually seen surrounded by polymorphonuclears Surrounding this area is a zone of granulation tissue containing histiocytes filled with lipoid. Leukocytes, plasma cells, and connective tissue cells form the abscess wall. When stained by hematoxylin and eosin, the granule of *A. bovis* exhibits a central basophilic area, irregularly circular, which is sometimes seen to be composed of closely packed, branching filaments about 1 micron in diameter. This dark area gradually shades into an acidophilic peripheral zone in which the filaments are distributed as though radiating from a central focus. Many of these filaments seem to be enlarged at their tips by being surrounded by a gelatinous sheath, forming "clubs." It is now thought that these enlargements are not formed by the fungus itself, but are contributed by the host, perhaps as a part of an immunologic mechanism, this view is strengthened by the observation of similar clubs around the causative fungi in other deep mycoses, notably coccidioidomycosis and sporotrichosis. The presence of well-formed clubs may be a valuable indication of a high degree of immunologic host resistance, hence, a good prognosis.

In Nocardia infections, granules may not be present (N. asteroides), and the organism will appear only as tiny branching filaments taking the basophilic stain. Gram's method reveals them more distinctly, and acid-fast staining may be definitive (*N asteroides*).

MYCOLOGY

Two types of fungi cause actinomycosis, anaerobic and aerobic, there is but a single species of anaerobe, *A bovis*, and at least four species in the aerobic group, Nocardia asteroides, N madurae, N. brasiliensis, and N paraguayensis

The anaerobic A bovis is the most commonly encountered Attention is usually called to its presence by the observation of tiny yellowish-white clumps of solidified material contained in the pus, the so-called "sulfur granules" of the "ray fungus" These may be seen more easily if the exu-

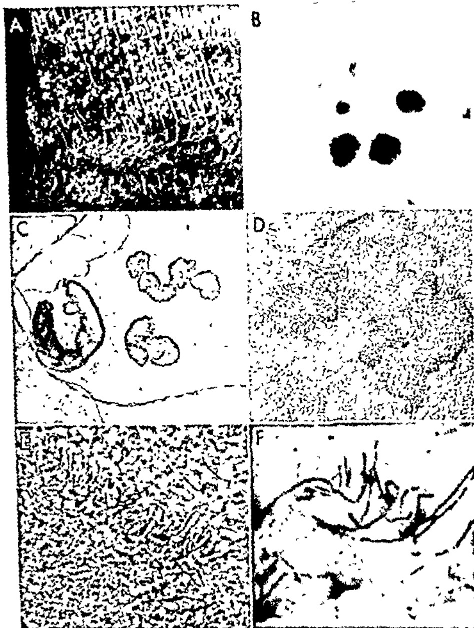


Fig 91 ***Actinomyces bovis*** **A**, granules caught in gauze dressing from draining sinus, × 4 **B**, granules in blood clot, × 30 **C**, hydroxide mount of various-sized granules, × 100 **D**, crushed granule, × 200 **E**, margin of granule showing club cells, × 400 **F**, crushed granule, with Gram-positive stain, × 1800

date is allowed to flow down the side of a test tube held against the light or to soak into the surface of a gauze pad or dressing. It is a fallacy, however, to assume that the discovery that pus contains solid particles identifies the disease as actinomycosis; similar granules are occasionally produced by bacteria of several types (actinobacilli) or may be composed of coagulated fibrinous material instead of organisms. The diagnosis must be confirmed by examining granules microscopically and culturing the causative organism from them. It is also wrong to exclude actinomycosis because the pus contains no granules; cultures may recover a definitive pathogenic fungus, such as N. asteroides which does not produce them.

A granule should be placed on a slide with a drop of saline solution and gently crushed under a coverslip. The central portion is composed of a mass of delicate filaments about as large in diameter as bacilli, but longer and exhibiting "Y-shaped" branching. At the periphery, some filaments are surrounded by a gelatinous sheath, forming "clubs", since they seem to be radiating from the center of the granule, its appearance led to the term "ray" (actino) fungus Not all granules show these clubs, and they are more pronounced in some than in others.

Another granule should be crushed and stained by Gram's method. A bovis is Gram positive (as indeed are all fungi which take the stain). The finding of tiny, branching filaments is diagnostic.

N asteroides does not form granules and must be identified by staining thin smears of pus by Gram's method and searching for scattered tiny branching filaments which closely resemble those of A. bovis. Further identification is furnished by discovering them to be acid fast, although they are not as tenaciously so as are tubercle bacilli It is well to caution against wrongly identifying branching filaments of fibrin as actinomycotic fungi, the former are usually thinner, longer, straighter, and of less uniform diameter, resembling cobwebs

N. madurae forms granules which resemble those of A. bovis, from which it can be differentiated only by cultural methods, although the clubs are said to be less pronounced and feather-like and the granules themselves sometimes reddish yellow. Unlike those of N. asteroides, its filaments are not acid fast N brasiliensis forms similar granules. N. paraguayensis forms dark-brown to black granules

Granules may be composed of larger filaments, up to 6 or 8 microns in diameter, these are obviously caused by fungi other than Actinomyces or Nocardia, they will be discussed later.

Since the clinical picture of actinomycosis can be due to either aerobic or anaerobic organisms, both types of media should be employed in all cases

A bovis is difficult to culture, and suspected material (granules, if present) should be inoculated simultaneously on several types of anaerobic media to enhance the likelihood of success. Long tubes filled beyond the halfway mark with veal infusion (broth or thin agar preparation) contain-

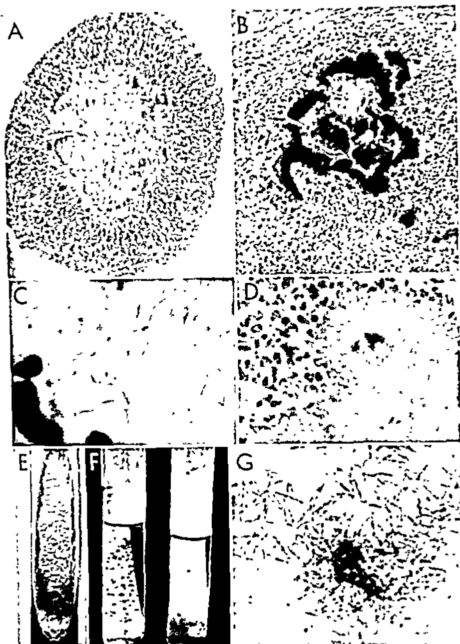


Fig 92. Actinomyces bovis. **A,** section through granule obtained from blood clot, × 55 **B,** granule in tissue, × 120 **C,** Gram-positive threads in interior of granule, × 1,800 **D,** club cells at margin of granule, × 600 **E,** cultural growth of Nocardia asteroides **F,** A bovis growing in thioglycollate broth, after two weeks **G,** culture mount with matted rods

ing 1 per cent glucose and adjusted to pH 7.4 are perhaps the best; Brewer's thioglycollate semisolid medium with dextrose is good. In such tubes the fungus grows as yellowish-white bacteria-like colonies; all are at least 2 cm. below the surface of the medium. On anaerobic plates, colonies are yellowish-white and small and may be rough or smooth. A. bovis is difficult to keep alive in such artificial cultures and usually does not survive many transfers. Occasionally, it seems able to adapt itself partially to aerobic conditions after subculturing

Suspected colonies must be pipetted from the deep tubes or removed from the plates by a loop and mixed with a drop of saline or lactophenol for the preparation of slides. Short rodlike forms resembling bacilli, often "diptheroid" in shape, are commonly seen, sometimes branching threadlike hyphae not over one micron in diameter are present. Similar preparations should be stained by Gram's method; as stated, A bovis is Gram positive.

N asteroides is usually easily isolated aerobically and at room temperature on Sabouraud's glucose agar, especially if blood is added. The colonies as a rule show no aerial filaments but remain yeastlike, becoming heavily wrinkled and heaped up as they age. The color varies from dark yellow through orange to coral.

Microscopic examination of bits of such colonies when young reveals a mycelium composed of fine branching filaments about 1 micron in diameter. Older colonies will yield more fragmented forms, resembling bacilli or cocci, and many chlamydospores. These elements are acid fast, although not as persistently so as are the Mycobacteria of tuberculosis or leprosy. They are more able to retain the stain in tissue sections than in culture. Some authors accord species status to a light-colored strain which becomes white with age because of the formation of a powdery aerial mycelium (N. gypsoides) This variety closely resembles N. brasiliensis except for the lack of enzymatic ability

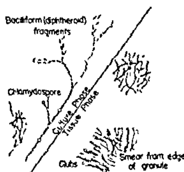
N brasiliensis is a common cause of Madura foot in Mexico and Central and South America Colonies are wrinkled, the color is yellow to orange, and the surface is covered with a white or tan chalky powder The filaments are slightly acid fast In contrast to N. asteroides, which it otherwise resembles, N brasiliensis has enzymatic ability to liquefy gelatin and coagulate milk.

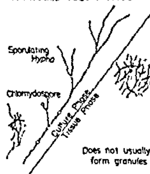
N madurae is easily cultured in the same manner as N. asteroides and grows as waxy, heaped-up, wrinkled masses, sometimes acquiring a powdery surface with age and varying from a cream color to purplish-red or orchid hues The more highly pigmented varieties have been called N. pelletieri by some authors, but Gonzalez Ochoa found them to have identical specific precipitin reactions with N madurae and considered them synonymous This fungus is not acid fast It has enzymatic ability to coagulate milk and liquefy gelatin

N. paraguayensis grows as a waxy, yeastlike mass with a light or dark-brown color. The filaments are not acid fast, and N paraguayensis is able

to liquefy gelatin and coagulate milk. Gonzalez Ochoa considered this species to belong to the genus Streptomyces

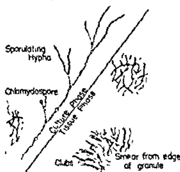
The differentiation between these four species of Nocardia is fairly distinct. Some authors divide these groups into more species. The reader is

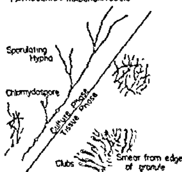




referred to the original articles for further discussion of this complicated subject, which is not as yet resolved.

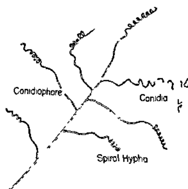
The mycology of maduromycosis is an extremely difficult, highly technical subject. In addition to the previously mentioned Actinomyces and





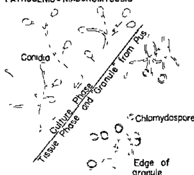
Nocardia species, more than 40 names have been utilized to designate certain fungi as separate and distinct species, each of which has been considered the cause of Madura foot in one or more instances Among these are several additional Nocardiae, 10 or more species of a genus of brown to black fungi, Madurella, the "granules" of which are black in the tissues ("black grain" Madura foot), common in India and occasionally recovered in the Americas, and species of Indiella, Glenospora, Cephalosporium, and

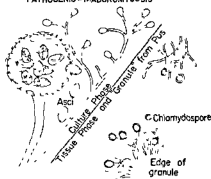
Acremoniella. The criteria for distinguishing these organisms one from another are not clearly drawn in many instances, the original authors must be consulted for further details Also blamed occasionally for Madura foot are representatives of several genera such as Aspergillus (and its subgenus,



Sterigmatocystis), Penicillium, and Mucor, whose role as pathogens is subject to doubt in view of their ubiquitousness as air-borne contaminants and the opportunity thus offered to them to become secondary invaders superimposed on other disease processes

Much more firmly established as a cause of Madura foot is a single





species of fungus, Monosporium apiospermum, the perfect stage of which was found by Emmons to be an Ascomycete, Allescheria boydii. Granules formed by this organism in tissues vary in color (white, red, or black), they may be distinguished from those due to A. bovis and the Nocardiae by having hyphae of much larger diameter (up to 5 microns), some of which

bear at the periphery of the granule pyriform conidia typical of the cultural phase of the fungus Growth is rapid in culture, the colony is at first white and fluffy, later developing a dirty-gray or brown tint. Examination of fragments of such colonies reveals the characteristic ovoid to pear-shaped conidia borne singly at the tips of conidiophores.

Attempts to classify and identify the fungi responsible for maduromycosis by the color exhibited by the granules in the tissues and pus have been unsuccessful, perhaps the color is not always produced by the fungus but may be produced by associated chromogenic bacteria.

Animal inoculation is seldom of assistance in identifying actinomycosis. In the absence of concomitant trauma or bacterial infection, the pathogenicity of the organisms for laboratory animals is of such a low degree as to be unreliable.

IMMUNOLOGY

The allergic and immunologic phases of actinomycosis have been extensively studied, but the reactions are not consistent and cannot be accurately correlated with its clinical course. Some of the discrepancies may be due to difficulty in the production of reliably uniform antigens or suspensions of the organisms It is probable also that considerable clarification could be obtained if the observers adapted their theories to comply with the results of the tests, rather than allowing the discrepancies to cause abandonment of the procedures as "useless."

Hypersensitivity has been demonstrated during actinomycosis by the response to the intracutaneous injection of culture filtrates, both local and systemic reactions occur. The significance of this reactivity is in doubt. Mathieson and co-authors expressed the belief that some persons develop allergic hypersensitization to A bovis because of repeated absorption of the fungus or its products from its saprophytic habitat within the body and that they thereby finally become susceptible to its pathogenic invasion They advanced this concept to explain the comparative infrequency of the actual infection when the organisms are so often present in normal persons It has been claimed also that by repeated vaccination with culture extracts, hypersensitive persons may be desensitized, and that during this process they develop specific immunity In this regard it is interesting to speculate on the possibility that some of the beneficial influence exerted by antibiotics upon the course of actinomycosis may be due to such a desensitization mechanism This theory seems especially plausible in the case of the antibiotics derived from fungi of the genus Streptomyces, which are closely allied phylogenetically to Actinomyces and Nocardia and might be expected to produce similar antigens

In contrast to this view, it must be pointed out that in some other deep fungous infections (notably coccidioidomycosis, histoplasmosis, and to a

lesser extent North American blastomycosis), the development of hypersensitivity is the rule rather than the exception and that the greater the degree of allergic reactivity of the patient's skin, the greater is the likelihood of complete recovery from the disease through development of immunity.

Especially significant in this regard is the work of Gonzalez Ochoa, who prepared a "purified polysaccharide derivative" from cultures of N. brasiliensis which appears to be highly specific in infections due to this organism In a series of such cases, hypersensitivity of the delayed tuberculin type was revealed by intracutaneous testing in all patients who resisted the infection sufficiently to become cured eventually, while those who succumbed were consistently nonreactive. This parallels experience with the prognostic significance of the coccidioidin skin test (also using a purified polysaccharide) and conforms to what seems to be a predictable trend in histoplasmosis and the blastomycoses. In all of these diseases hypersensitivity appears to parallel the patient's ability to resist the progress of the infection immunologically; hence, artificial desensitization would seem to be illogical and perhaps dangerous. Further clarification of this subject is necessary before much reliance should be placed in vaccine therapy, or indeed before its administration should be considered safe.

Complement-fixing antibodies as well as agglutinins and precipitins have been demonstrated in the sera of persons infected with actinomycosis, but not consistently or with enough specificity to warrant the use of such procedures for diagnostic or prognostic purposes.

It is worth pointing out that these discrepancies may actually be due to attempts to fit the results of the tests into the observer's preconceived ideas of their significance instead of allowing them to speak for themselves Perhaps the precipitin and complement fixation tests actually should be interpreted as they are in coccidioidomycosis, in which disease they appeared to be equally irregular until better interpretation revealed them to be consistently valuable. Also, there is a wide variation in the antigens as prepared by different observers, and some uniformity will be necessary before the subject can be clarified A single observer rarely has the opportunity to study enough cases to draw conclusions.

DIFFERENTIAL DIAGNOSIS

Actinomycosis in general must be differentiated from tuberculosis, neoplasm, syphilis, staphylococcic cellulitis, osteomyelitis, and all the other deep mycoses The cervicofacial form may resemble glanders or bacterial infections arising from dental lesions, such as the burrowing sinuses derived from apical abscesses Abdominal actinomycosis may simulate chronic appendicitis, amebiasis, liver abscess, salpingitis, or pyelonephritis The pulmonary form must be differentiated from sarcoidosis, neoplasm, and bacterial lung abscess

PROGNOSIS

The outlook is best in the cervicofacial type of actinomycosis and poorest in the abdominal form. Madura foot seldom threatens the life of the patient but frequently necessitates amputation of the limb.

TREATMENT

There is no doubt that the advent of the sulfonamides and the antibiotics has bettered the prognosis of actinomycosis, but none of these alone nor any combination of them should be considered as specifically curative without adjunctive therapy. Initially, dramatic improvement follows their use, but soon a point is reached beyond which further progress is extremely slow, even though adequate dosage is continued. It is true that the discontinuance of such medication is frequently followed by exacerbation and its readministration by improvement, which seems to indicate that it is capable of holding the activities of the fungus in check. It seems more likely, however, that most if not all of the effect of the substances should be attributed to their ability to combat bacterial infection and thus deprive the fungus of the symbiotic alliance which has been previously alluded to as one of the principal reasons for its acquisition of pathogenicity. It is true that in vitro certain strains of A. bovis seem susceptible to one or another drug, but it must be recalled that cultures of this organism are not easily obtained or maintained in vitro even without such antagonistic substances. Selection of medicaments by such "specific testing" is permissible, but it is even more important to investigate in the same manner the bacterial flora which also is present and administer the appropriate drugs to combat this factor as well Nocardiosis apparently responds better to sulfonamides than to antibiotics, the opposite is true of A bovis infections Neither form of chemotherapy helps the other forms of maduromycosis appreciably. Isoniazid has been recommended for A. bovis infections by McVay and Sprunt. Gonzalez Ochoa advised 4,4-diamino-diphenyl sulfone for disease caused by N brasiliensis

Vaccine therapy has been advocated by several workers, but this subject needs further cautious investigation in the light of the view that such procedures may actually be harmful

After the initial amelioration is obtained by "specific drugs," surgical drainage should be adequate, and all tissue manifestly beyond recovery should be debrided Intelligent use of antibiotics permits the surgeon more latitude in his procedures.

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cially in the cervicofacial type

It is extremely important to point out that the factor responsible for the ultimate complete eradication of the disease is almost certainly the body's natural ability to resist and heal the infection, whether by the development of specific immunity, phagocytosis, or some other mechanism. Prolonged rest in bed, adequate nutrition, and multiple vitamin supplements, especially of the B complex series, are vital

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28. Sporotrichosis

FROM an exogenous source in nature exhibiting but little geographic limitation, human beings occasionally become inoculated with the pathogenic fungus Sporotrichum schenckii, usually percutaneously by means of a puncture wound. A syndrome develops which so closely resembles the primary stage of syphilis that it is termed "chancriform." Much more rarely, a generalized type of infection occurs Correlating this disease in its typical and atypical forms pathogenetically with the other deep mycoses seems destined to yield considerable improvement in our understanding of mycotic infections in general. However, sporotrichosis is usually acquired by direct inoculation through the skin in contrast to what occurs in most other deep fungous infections

HISTORY

The first report concerning sporotrichosis in man was that of Schenck in 1898; it was so conclusive that his name has been accepted for the species epithet of the organism. However, according to Pallin, in 1881 Chénier had differentiated from true glanders a syndrome in horses called pseudofarcy, which was almost certainly sporotrichosis. In 1903 appeared the first of a large series of important papers by de Beurmann (in collaboration with Ramond, Gougerot, and others) in which the less common generalized form was first described. More than a hundred cases had been reported by 1910, when Hyde and Davis published an extensive review with a bibliography of over 150 references.

The discovery that sporotrichosis was frequently acquired from injuries sustained by contact with timbers in mines in South Africa was first reported in 1927 by Pijper and Pullinger, who cited 14 cases. By 1941, Dangerfield and Gear had collected 74 such cases. Subsequently, up to 1944, Helm and Berman recorded 2,825 additional cases From the study of such a wealth of clinical material an extremely valuable monographic symposium was prepared by the Transvaal Mine Medical Officers Association and published in 1947

ETIOLOGY

Although there is considerable morphologic variation among strains, it is usually accepted that sporotrichosis is caused by a single species of fungus, Sporotrichum schenckii.

DISTRIBUTION

Sporotrichosis has been reported from all areas of the globe where there is personnel capable of making the diagnosis. Certain circumstances enhancing the growth of the fungus in a particular environment, coupled with certain types of employment affording additional opportunities for sustaining puncture wounds, have caused epidemics in several instances, the most extensive of which is that previously mentioned as occurring in the South African mines. In Europe the majority of cases have occurred in France, in North America the northern portion of the central states area has the highest incidence

No age is exempt and there seems to be no variation in susceptibility because of race There is a distinct predominance in males, however, and in the age groups between 20 and 50 years, almost certainly attributable chiefly to occupations which subject them to trauma from materials bearing the fungi This view is confirmed by the high incidence in farmers, laborers, miners, and gardeners That local conditions are influential, however, is evidenced by the report of Padilha Gonçalves and Peryassu, who observed a higher incidence in females.

EPIDEMIOLOGY

The source of sporotrichosis in nature is usually vegetation, living or dead Many species of Sporotrichum are common saprophytes on vegetation and in animal excreta. Sporotrichum schenckii has been cultured artificially on carnations by Benham and Kesten. Foerster was able to trace many cases to the thorns of the barberry shrub Sphagnum moss was found to be the focus in six cases in florists by Gastineau, Spolyer, and Haynes. Singer and Muncie found the organism on hay used on horticultural farms where several cases had originated Infections have occurred in laboratory workers from handling cultural growths Sporotrichosis has been observed frequently in horses and less often in cats, dogs, rats, and mice, and human infections have been attributed to such sources Smith accepted a lesion on the cheek of an infant as having occurred by direct transfer from the infected cheek of the mother, the only instance of human to human transference

Investigating a tremendous epidemic originating in a South African gold mine, Brown was able to develop a technique which demonstrated the fungus on a large proportion of samples of the timbers supporting the mine

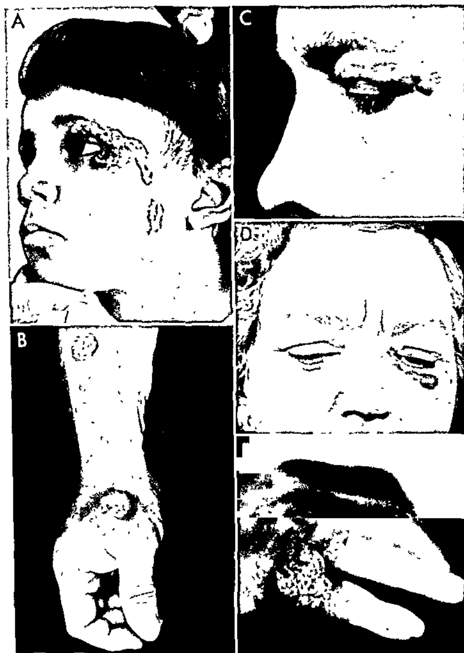


Fig 93 Sporotrichosis A, granulomatous lesions in linear distribution on eyelids and cheek B, nonulcerative infiltrated plaques in a caretaker C, diffuse lesion on upper eyelid D, involvement of lower eyelid E, verrucous, moist, localized tumefaction

shafts. (*See also* under subhead "Mycology," p. 280). She found the organism as a heavy mat closely applied to the surface of the timber and thickly overlain by a growth of saprophytic molds. The fungus was found only where the temperature range was from 79 to 84 F. and the relative humidity from 92 to 100 per cent.

The vast majority of all recorded cases of sporotrichosis have followed a course indicating that the fungus was inoculated into or through the skin from a wound caused by contact with contaminated material. According to Dangerfield and Gear, the incubation period varies from three days to three weeks, and is usually about one week. The resulting infection remains localized, extending at the most only to the adjacent lymphatic structures In a few instances the initial source of infection has been obscure, usually being attributed to ingestion or inhalation of the organisms. Apparently, it is in this group that the disseminated form of the disease has been observed.

CLINICAL CHARACTERISTICS

In their extensive writings, de Beurmann and Gougerot classified sporotrichosis into six clinical types, lymphatic, disseminated, epidermal, mucosal, skeletal, and visceral, although many cases admittedly presented lesions belonging in more than one of these groups Clinical syndromes duplicating all of these have long been observed in other deep mycoses, particularly coccidioidomycosis, North American blastomycosis, and histoplasmosis, but in these diseases no such six types are considered as separate entities. The localized type resulting from direct primary inoculation of the fungus into the skin is certainly distinct, as is the disseminated form; most of the other classes are probably variants of one of these and will be treated as such here.

1. Primary cutaneous sporotrichosis.—This results from inoculation of Sporotrichum schenckii directly into the skin. Usually there is a history of a puncture wound or an abrasion, but penetration of intact hair follicles is considered probable in some instances A chronic infection of the skin develops at the point of inoculation, usually becoming ulcerative. The incubation period is generally thought to be from three to 21 days, but it apparently may be delayed several months After studying 2,825 cases, Helm and Berman reported that the initial lesion appeared on the hand or arm in 60 per cent, on the trunk in 23 per cent, on the legs in 11 per cent, and on the face or neck in 2 per cent. Multiple initial lesions were present in 4 per cent. In their series no such lesions originated in the scalp, bathing trunk area, or feet, admittedly because these areas were protected by such clothing as is worn by native laborers in the mines

Most frequently the lesion first appears as an elevated pustule, pink or cyanotic, frequently oval, with the long axis directed in line with the natural skin creases There is no pain unless secondary bacterial infection is

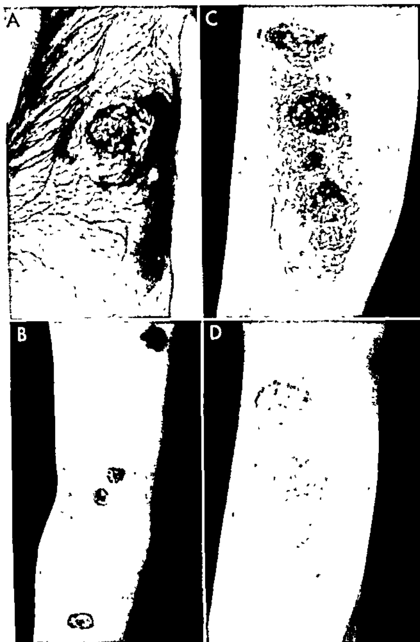


Fig 94. Sporotrichosis. **A,** initial lesion, or chancre, which has become ulcerated **B,** ulcerated, granulomatous lesions which developed proximally along forearm. **C,** nodular lesions which were incised in mistaken belief that they were pyogenic **D,** final result, which was poor.

present. A small amount of pus can usually be expressed This lesion slowly enlarges and forms an ulcer with a bright-red base free of necrotic tissue and with ragged undermined edges Bleeding is easily induced Small secondary papules usually surround the ulcer.

After a week or more, in the majority of patients nodules develop along the draining lymphatic channels, small at first, but rapidly enlarging to form abscesses; surprisingly, the nodule farthest from the original lesion is frequently the more advanced. The lymphatic vessels themselves are often reddened and indurated. Unless treatment is administered, these nodules tend to ulcerate and may even coalesce. The regional lymph nodes rarely become palpable and never ulcerate There is little tendency toward complete spontaneous cure, but this form of the disease apparently never spreads beyond the regional lymph nodes. The general health of the patient is usually not affected, even fever as a rule being absent.

Some patients never have lymphatic lesions, but the disease may spread in the skin itself, forming a flat plaque, either smooth or covered with silvery scales. A warty form is sometimes seen, oftenest on forehead or knee Sometimes extensive fungating, warty, and pustular lesions develop, simulating blastomycosis or verrucous tuberculosis (Smith and Garrett) These variations are thought to be due to various factors, such as local tissue resistance, general body resistance, and the depth of the inoculation Experimental infections in human beings are said by Helm and Berman to suggest that intradermal inoculation produces a superficial, mild lesion, while the subcutaneous route produces the pustular ulcerative variety.

Because of resemblance to the primary lesion of syphilis, the primary cutaneous type of sporotrichosis, as stated, is termed "chancriform" As pointed out in the appropriate chapters, this is the analogue of the type of infection which has been observed when Coccidioides immitis and Blastomyces dermatitidis was inoculated into the skin in exactly the same manner, such a reaction is also considered probable in histoplasmosis (Curtis and Harrell) This is not surprising in view of the similarity to the syndrome observed under the same circumstances in tuberculosis, yaws, and American leishmaniasis Thus it appears that the route by which all these infections are acquired bears a profound relationship to the type of clinical syndrome which results Coccidioides, Blastomyces, and Histoplasma form spores so easily dislodged from their sources in nature as to blow in the wind to be inhaled, seldom are they inoculated into the skin. Sporotrichum grows as a moist mat, closely adherent to its substrate vegetation and hence is seldom inhaled but is frequently inoculated intracutaneously Whereas at first glance there seems to be a great deal of difference between the manifestations of sporotrichosis on the one hand and coccidioidomycosis, blastomycosis, and histoplasmosis on the other, it appears likely that they actually resemble each other very closely provided only that they are acquired through the same portal of entry The fact that each disease is seen almost exclusively in its predominant form, while

occasionally duplicating the other type, is easily understood in the light of this concept.

Sporotrichosis has been observed beginning in the mucous membranes of the nose, mouth, or pharynx Sometimes it subsequently follows the syndrome typical of the primary cutaneous type, resulting in regional lymphatic involvement in a manner suggesting primary inoculation into those membranes Other cases seem to indicate that the origin of such lesions is by dissemination, since other organs are simultaneously found to be involved.

2. NONTEGUMENTARY PRIMARY SPOROTRICHOSIS.—If the concept outlined above is correct and only the chancriform type of infection limited to the regional lymphatics can result when the skin is the portal of entry, the existence of a primary inoculation type of sporotrichosis with a way of entry other than the skin must be accepted to explain the disseminated form, but conclusive proof is difficult to obtain. No large reservoir has been discovered of persons reacting positively to "sporotrichin," indicating thereby the probability of an unrecognized benign systemic infection sometime in the past, as is the case with histoplasmosis and coccidioidomycosis. De Beurmann showed that the organism could pass through the intestinal mucosa when ingested on contaminated raw fruits or vegetables, but cases of gastrointestinal tract involvement are rare. Simson reported that the infectivity of cultures was retained, although in lessened degree, after two years of drying, and the fungus was recovered once on a plate exposed to dry air in a mine shaft, indicating at least the possibility of an inhalational route of infection. Until further data are available, it is necessary to consider this entity only vaguely, as has been done here, and pass on to what is probably its sequel, the disseminated type.

3. DISSEMINATED SPOROTRICHOSIS —First it is necessary to differentiate "dissemination" from the rather extensive spread to regional lymphatic structures of the typical intracutaneously acquired form In contrast, by dissemination we here mean the scattering of the disease over the body into other areas by organisms transported in the blood stream

Disseminated sporotrichosis is observed but rarely, although it is likely that some cases exist which are never correctly diagnosed. The majority of instances were reported in the earlier years from France, where the incidence appears to have decreased of late Foerster, Moore and Kile, Collins, and Cawley have recorded this type in America The manner in which the infection was acquired has usually been obscure, but enough instances of involvement of mouth, pharynx, or lungs have been observed to suggest that these routes are the likely ones Again, the resemblance to coccidioidomycosis, blastomycosis, and histoplasmosis similarly acquired must be considered significant.

Especially worthy of emphasis is the fact that no case of such dissemination was encountered in the entire series of 2,825 cases studied in the South African mines, where conditions were such that the intracutaneous

route was almost certainly the only one through which the infection was acquired. Nor can any authentic case be discovered in the writings of other authors (de Buermann, Collins, Foerster).

In its commonest form, *disseminated sporotrichosis begins as multiple* subcutaneous firm nodules scattered over the body; these seldom ulcerate spontaneously but become abscessed and after incision or traumatic rupture form chronic ulcers. From these the infection tends to spread to involve larger areas of the surrounding skin, simulating the lesions of *tertiary syphilis, tuberculosis*, or other deep fungous infections. There is little tendency toward spontaneous cure, and response to therapy is variable. Some cases progress rapidly to death, while others remain chronic for months.

Associated with this syndrome (or even without it in some cases), there may be involvement of bones, joints, muscles, tendon sheaths, lungs, genitourinary system, or other viscera. Hyslop *et al.* even reported central nervous system infection, but they were unable to prove the diagnosis culturally and therapy was unsuccessful.

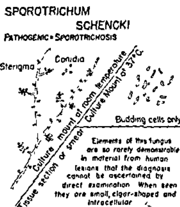
PATHOLOGY

The gross pathology of both the primary cutaneous (chancriform) and the disseminated type of sporotrichosis may be surmised from the clinical picture, there is no useful point of differentiation from similar entities except the tendency for nodules to develop along the lymphatic channels in the former, and even this characteristic is duplicated by coccidioidomycosis and blastomycosis in the primary cutaneous form.

The most important feature in which human sporotrichosis differs from most other infectious diseases is the practical impossibility of ascertaining the diagnosis in the primary cutaneous form through discovery of the causative organisms in tissues by histopathologic study This situation is somewhat difficult to explain, since sections of heavily infected tissues of experimental animals as well as those from the viscera of the disseminated type in human beings, when stained by hematoxylin and eosin or the periodic acid-Schiff technique, reveal the organisms in large numbers and show them to be tiny (3 to 5 microns in length) cigar-shaped bodies which bear from one to three small oval buds at either or both poles. It is probable that in human tissue of the chancriform type the fungi are actually present, either in the form described in animals or in some other "coccoid" stage, but that they remain undiscovered because they are too small, too sparsely distributed, or too poorly defined to be differentiated from cellular debris Fortunately, cultural methods as a rule are easily successful in demonstrating their presence, the procedure affords one of the best of reasons for insisting on the inoculation of cultures from all pathologic material as a routine measure whenever diagnosis is obscure, *and this before the tissues* are placed in fixing solutions Histopathologic preparations should be care-

fully studied, however, because it is frequently possible to exclude sporotrichosis by demonstrating some other infectious organism as the cause, since the other fungi are usually easily seen and recognized.

merging into a chronic granulomatous layer of fibroblasts and giant cells. A sporotrichotic nodule tends to show several more or less distinct concentric zones, the central one composed of an anuclear mass of necrotic material which is sometimes purulent, surrounded by polymorphonuclear leukocytes, merging into a zone of fibroblasts, lymphocytes, epithelioid



cells, and giant cells Simpson, Helm, and Bowen emphasized the presence of eosinophils in the majority of cases, whereas Satenstein was impressed by the large number of mast cells Except for the presence of concentric zones, the granulomatous picture cannot be differentiated from that of syphilis, tuberculosis, or the other deep mycoses.

MYCOLOGY

Sporotrichosis is caused by a single species of fungus, Sporotrichum schenckii (Matruchot, 1910) in the opinion of the majority of authors. There have been several attempts to delineate separate species because of the wide variations in morphology encountered in artificial cultures, but equally wide differences have been observed in subcultures originating from single strains. This view is confirmed by Lurie's studies on metabolism Particularly variable is the color, ranging from creamy white through shades of brown to black

Except in infections in experimental animals, and perhaps in the heavily infected tissues of human beings in the disseminated stage of the disease, direct examination of exudate or tissue juices will usually not

serve to demonstrate the causative organisms. This situation is probably due to their small size and variable shape and the ease with which they may be confused with debris, but it is also likely that they are not present in large numbers in the usual type of sporotrichosis encountered clinically. Occasionally the "asteroid" form has been seen and correctly identified, but it must be recalled that a similar morphologic entity has been seen in other deep mycoses, notably coccidioidomycosis, blastomycosis, certain bacterial infections, and, of course, actinomycosis

1. CULTURAL CHARACTERISTICS.—Fortunately, Sporotrichum schenckii is easily recovered in culture, and this procedure thus becomes the mainstay of diagnosis. It is well to inoculate pus as well as small fragments of biopsy tissues upon a variety of media, including blood agar and Sabouraud's glucose agar, with and without additives such as cyclohexamide to inhibit bacterial overgrowth Specimens of each type of inoculation should be maintained at room temperature as well as 37 C. Growth is usually noticeable within a few days.

At room temperature, the colony begins as a moist, adherent, creamy-white mat without aerial mycelium As growth continues, most strains turn dark brown or black, and the surface becomes heavily wrinkled To the initiated eye there can be confusion with no other pathogenic fungi and with only Pullularia among the common contaminants Microscopic examination of colonies reveals them to be composed of unusually narrow hyphae, about 2 microns in width, bearing numerous small pear-shaped or rounded conidia in grapelike clusters or along the sides of the hyphae, each at the tip of a short threadlike sterigma so thin as to be invisible unless carefully searched for These sterigmata are the most definitive feature in identifying this genus of fungus. Brown, Weintroub, and Simson described triangular spores, 2 to 5 microns on an edge and with convex surfaces causing them to appear oval in cross section, seen in colonies as well as when the fungus was growing on the surface of wood. When searching for the fungus in nature, they found the presence of these spores to be a helpful clue

At 37 C , the colonies resemble those of bacteria, varying in color from creamy white to dirty brown or gray. Microscopically, only yeastlike budding cells are seen, with occasional abortive attempts to form hyphal threads Some cells are cigar shaped (fusiform) and bear the blastospores at one or both extremities, singly or in pairs or trios, resembling the forms seen in animal tissue sections Some cells are oval or round and up to 5 microns in diameter Exceptionally large forms have been described in tissues and cultures derived from South African cases.

2. ANIMAL INOCULATION —Intraperitoneal injection into mice or rats causes a nodular type of peritonitis, smears from which will reveal the organisms in the yeastlike pathogenic phase previously described Extensively studying intraperitoneally infected rats, Simson and Brandt described the organisms in five stages. (1) cigar shaped, (2) rounded

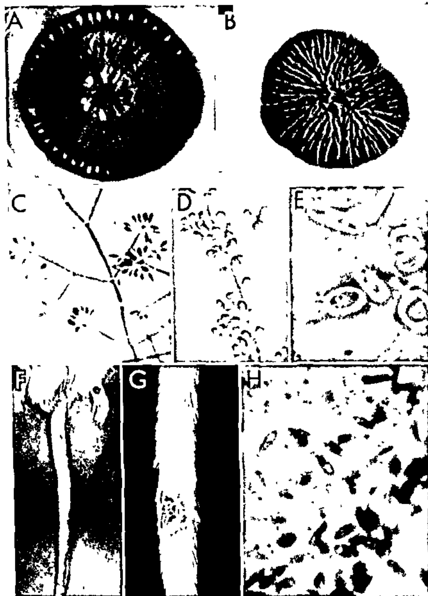


Fig 95 Sporotrichum schenckii. A, giant colony of recently isolated strain after one month, jet black color is typical B, after repeated subcultures, pigment may be lost

Cornell University Medical College)

(cryptococcal), (3) spherical with doubly contoured border, (4) the same surrounded by a mantle of acidophilic material, and (5) the fully developed asteroid form. They concluded that the material composing the asteroid rays is a protective mechanism of the fungus against the tissues of the host, suggesting that this form is seen only when there is resistance actually being offered by the host. The view suggested in considering the same structure when encountered in coccidioidomycosis, that this acidophilic material is really contributed by the host, seems equally applicable and similarly significant of host resistance.

IMMUNOLOGY

Subsequent to the recent reports indicating that when either Coccidioides or Blastomyces dermatitidis is inoculated intracutaneously a chancriform syndrome results comparable to the common form of sporotrichosis, it has become increasingly interesting to compare these diseases in other ways as well. If the immunologic reactions observed in these three infections are indeed closely parallel, an explanation is at hand for some of the heretofore "unreliable" results reported concerning the reactions to "sporotrichin"

That the body resists the invasion of S schenckii when it is intracutaneously inoculated is evidenced by the intense cellular response both locally and throughout the adjacent lymphatic structures. This resistance is not complete, however, since the infection extends to involve the entire limb before becoming arrested and complete spontaneous cure seldom occurs

Antigenic materials extracted from cultures of S schenckii have been investigated, but not yet as extensively as have similar materials in coccidioidomycosis. Agglutination was described by de Beurmann and by Moore and Davis, more recently Du Toit was able to show that normal serums could cause sporotrichum spores to agglutinate in the same manner.

Intracutaneous injection of sporotrichin has yielded variable results, Bloch considered a positive reaction of diagnostic value, de Beurmann interpreted a negative test as excluding sporotrichosis but found some "false positive" reactors, Du Toit stated that a positive reaction regularly occurs in patients with sporotrichosis, Gonzalez Ochoa, Padilha Gonçalves, and Pontes de Carvalho agreed. In an infection experimentally produced in a volunteer, the response developed on the fifth day following inoculation All of these findings are consistent with experience in coccidioidomycosis except that it is now accepted that the "false positives" in that disease occur almost exclusively in persons who have had the infection, even though it was never perceptible clinically, and have recovered, perhaps this is the case in sporotrichin testing also Better purification of the antigen, particularly directed toward use of only a pure polysaccharide fraction for skin testing, would probably eliminate other false positives, due to protein components (Gonzalez Ochoa) Simson et al found many persons in

whom an infection could not be induced by experimental inoculation of S schenckii, a fact indicating that they were immune; it is not stated whether these persons were tested with sporotrichin, but experience with coccidioidin testing would lead us to expect that they would react positively if the immunity was of the acquired form. These authors also observed that infections which followed inoculation of the organisms in persons already harboring the disease were milder and cleared more quickly than usual, an observation indicating that a significant degree of resistance can be acquired

The complement fixation test has also given variable results. Norden found it positive in only two of 11 cases, the titer not being stated This is not surprising if the reaction follows the pattern which seems to be established in coccidioidomycosis and blastomycosis and to be developing in histoplasmosis, in which the titer parallels the total quantity of involved tissues (or, in a later view, the total number of organisms actively engaged in producing the disease at that moment). In the cases of known primary cutaneous blastomycosis and coccidioidomycosis which have been recorded, the reaction to the complement fixation test has also been negative or low in titer and transient In cases of disseminated sporotrichosis, however, the titer might be expected to be high and the intracutaneous reaction weak or negative (anergic), in conformity with the poor prognosis and providing a situation in which a negative reaction to the skin test would not rule out the diagnosis of sporotrichosis

A precipitin reaction has been reported, but its significance is not yet clear. In experimental animal infections it is routinely demonstrable, as in coccidioidomycosis when the same test is done within the first few months of the inoculation.

It is evident that much additional data are needed before these tests can be evaluated One pitfall which must be avoided is that of anticipating the same results from all of these different procedures in a given patient at a given time, i e, all tests negative or all tests positive. The tests do not parallel each other in coccidioidomycosis and it is evident that each reveals the presence of a different antibody and that each is of different significance in the prognosis. It appears likely that similar conditions will be found to prevail in sporotrichosis. (*See also* Chapters 29, "North American Blastomycosis," and 32 "Coccidioidomycosis."

DIFFERENTIAL DIAGNOSIS

Primary cutaneous sporotrichosis should be suspected whenever a wound in the skin becomes chancriform and is accompanied by regional lymphangitis, without fever, and lymphadenopathy, especially if the original injury was acquired from a plant, thorn, or timber. If, in addition, nodules are seen along the course of the lymph vessels draining the area, the diagnosis is almost assured, barring a rare case of the primary cutane-

(*cryptococcal*), (3) *spherical with doubly* contoured border, (4) the same surrounded by a mantle of acidophilic material, and (5) the fully developed asteroid form. They concluded that the material composing the asteroid rays is a protective mechanism of the fungus against the tissues of the host, suggesting that this form is seen only when there is resistance actually being offered by the host The view suggested in considering the same structure when encountered in coccidioidomycosis, that this acidophilic material is really contributed by the host, seems equally applicable and similarly significant of host resistance.

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X radiation in semi-intensive dosage, with 3 mm. aluminum filtration, is a useful adjunct and may be administered to carefully shielded lesions, particularly to solitary lesions.

Surgical intervention is rarely necessary or desirable. To incise a lesion ensures that the patient will later have a linear scar. It may also allow the entry of bacteria to complicate the problem. Such misguided treatment is usually practiced in the mistaken belief that the patient has a pyogenic lesion If fluctuation develops, simple aspiration will suffice

TABLE 10.—Dosage Schedule of Potassium Iodide in Treatment of Sporotrichosis*

Day	Breakfast	Lunch	Dinner	Total
1	10	11	12	33
2	13	14	15	42
3	16	17	18	51
4	19	20	21	60
5	22	23	24	69
6	25	26	27	78
7	28	29	30	87
8	31	32	33	96
9	34	35	36	105
10	37	38	39	114
11	40	40	40	120

* Numerals refer to drops of saturated solution, which should be well diluted with water or milk and taken after meals

Vaccines prepared from cultures of the yeast phase have been suggested to supplement iodide therapy when progress is slow, their status is questionable, as in other deep mycoses

The tetracycline drugs may be of some help in recalcitrant cases Penicillin and streptomycin are ineffective

In early cases, hot wet fomentations with a saline solution may be of slight help For open lesions, aqueous gentian violet 1 per cent or half strength Lugol's solution may be applied once daily.

Pain is sometimes a troublesome symptom Acetylsalicylic acid usually suffices, although codeine or meperidine (Demerol) may be required until the effect of the iodide therapy is obtained

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ous form of one of the other deep fungous infections. The primary stage of syphilis, tuberculosis, yaws, and American leishmaniasis may be confused with this form.

Disseminated sporotrichosis is difficult to differentiate from neoplasms, tuberculosis, syphilis, and other deep mycoses.

In either form of the disease all doubt can usually be dispelled within a few days by cultural methods.

PROGNOSIS

Even without treatment, the primary cutaneous, chancriform type of sporotrichosis remains limited to the region of the body adjacent to the inoculation site, but spontaneous complete recovery is not to be expected The response to specific therapy is usually very satisfactory.

Disseminated sporotrichosis is always dangerous and responds less well to similar therapy

TREATMENT

It may not be necessary to hospitalize every patient suspected of having sporotrichosis. There is some advantage, however, in observing the patient carefully, and this cannot always be accomplished on an ambulatory basis. At first, the diagnosis may be in some doubt and the facilities for investigation should be the best obtainable Another important consideration is the tolerance of the patient to medication. This is best determined in a hospital Once the treatment has been well started, there is little need for more than supervisory care with observation of the patient every few days.

It has long been known that potassium iodide is almost a specific drug in sporotrichosis No drug has yet been developed as an adequate replacement The accompanying table suggests a plan for use of the drug and a convenient way to record the dosage In order to safeguard against acute iodism, it is imperative to begin with a dose no larger than 10 drops of the saturated solution Some experienced clinicians prefer to start with 5 drops As shown in the table, the increment of drug is 1 drop per dose By the 11th day, a single dose of 40 drops is reached. This is usually continued three times daily for at least two weeks If all signs of the active disease have then disappeared, a descending dosage may be arranged, extending over 11 days and ending with the beginning dose Potassium iodide should always be taken with food in the stomach In patients in whom symptoms of gastritis develop, the demulcent drugs, as in the treatment of gastric ulcer, should be prescribed to take with the iodide The dose schedule should be reviewed and perhaps modified by skipping one or two doses and then resuming with 10 drops less than the amount which caused difficulty As an alternative, intravenous administration of sodium iodide may be considered This should be carried out cautiously with an ascending dose up to 1 or 2 Gm daily Thrombosis of veins is not uncommon.

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29. North American Blastomycosis
(Gilchrist's Disease)

THE fungus Blastomyces dermatitidis causes in the human body a rare, chronic, *suppurating granulomatous disease exhibiting* two widely divergent clinical pictures. In one form, apparently the skin alone is involved for many years without the general health of the patient being affected. In the other, the lungs are the primary focus, from which the disease as a rule soon becomes widely disseminated, usually causing death. When the term blastomycosis is used in the United States without modification, it designates this disease

HISTORY

To The American Dermatological Association in 1894, Gilchrist presented a preliminary report of the first case of North American blastomycosis, including a good description of the fungus as seen in the tissues In 1896 he published a detailed study of this case, and in collaboration with Stokes in 1898 he named the organism Blastomyces dermatitidis Numerous similar cases were discovered during the succeeding years, among which were some indicating that this organism was being confused with other fungi having a spherule stage in the tissues and capable of causing a deep infection (Cryptococcus, B brasiliensis, Coccidioides) Benham clarified the issue in 1934 by emphasizing methods by which these diseases could be differentiated

ETIOLOGY

It is generally accepted that a single species of fungus causes North American blastomycosis Its original botanical classification as Blastomyces dermatitidis is still preferred by most authors, although many accept it only with reservations

DISTRIBUTION

North American blastomycosis is an appropriate name, since the disease is limited practically if not entirely to that continent. Indeed, in the vast majority of instances it has originated in an even more restricted geographic area, the North Central States of the United States, in the upper portion of the Mississippi River Valley and the Great Lakes region. It has thus acquired the nickname "Chicago disease."

No age is exempt, but over half of the cases have occurred between the ages of 20 and 40. As is so common with the deep mycoses, males outnumber females, in this instance almost 15 to one There is no apparent racial hypersusceptibility.

EPIDEMIOLOGY

Although it is obvious that infection with B. dermatitidis follows acquisition of the fungus from some exogenous source, the reservoir in nature has not been discovered. Stober's early report that the fungus had been cultured from wood has never been confirmed

The exact manner in which the fungus enters the body is somewhat in doubt. Many cases originate in the lungs, most likely by the inhalation of dust containing spores. Although the fungus has not been found in specimens of soil in which it was suspected, Emmons has shown that sterilized soil will support its growth. Aspiration of material from the throat or mouth must also be suspected, although the presence of the organism in these areas has never been demonstrated in the absence of actual infection

In the commonest form of the disease, that in which it first appears in or just beneath the skin and remains localized there, extending but slowly by contiguity for years, it has always seemed logical to conclude that the organisms had been traumatically inoculated from an outside source directly into the skin at that point. Recent evidence makes this conclusion seem unwarranted, since it now appears likely that such inoculation results in an entirely different syndrome. This subject will be discussed in more detail under "Clinical Characteristics" in succeeding paragraphs

There are three instances in which the infection was acquired from a cadaver during autopsy and one in which it was acquired from laboratory cultures (*see* below under "Primary Cutaneous Blastomycosis") Ramsey and Carter reported 16 cases of blastomycosis in dogs, in most of which there were pulmonary as well as cutaneous lesions, but there are no known instances of transmission of the disease from dog to man Recently, 11 cases of pulmonary blastomycosis have originated within a small geographic area in North Carolina (Smith, Harris, Conant, and Smith). This epidemic, although small, is extremely important in a disease hitherto so sporadic and rare. Studies in the locality are being continued and seem to promise additions to our epidemiologic understanding.

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Fig 96. Blastomycosis in an Italian-American railway construction worker. A and B, in 1941, disease had been recurrent for 18 years Note involvement of eyelids and beginning ectropion Superficial ulceration and crusts may be seen C and D, in 1948, a few weeks before death, lesion over left scapula represents an extension of disease from lung Skin of face and chest was almost free of infection

CLINICAL CHARACTERISTICS

It has been customary to describe North American blastomycosis under the two clinical types which have been recognized for so many years and named "cutaneous" and "disseminated." Recent developments seem to warrant the different approach which has been adopted here, admittedly perhaps prematurely, which utilizes four divisions, primary cutaneous, chronic localized cutaneous, pulmonary, and disseminated. It appears likely that the latter three classes overlap considerably and are perhaps but different manifestations of the same process.

1. PRIMARY CUTANEOUS BLASTOMYCOSIS.—Schwarz and Baum first advocated the view that inoculation of B. dermatitidis directly into the skin of a previously uninfected person did not result in the common chronic cutaneous form of the disease so well known for so many years but caused a "chancriform" syndrome. They cited briefly three instances in which physicians had acquired the infection percutaneously and subsequently had an ulcerative papule at the site of the inoculation, followed by regional lymphangitis and lymphadenopathy. Wilson, Cawley, Weidman, and Gilmer reported these cases in more detail, adding another and emphasizing that this syndrome is logically acceptable as that to be expected from primary cutaneous inoculation, since it is almost exactly analogous to the clinical picture which results when the skin is directly inoculated with the organisms of tuberculosis, syphilis, American leishmaniasis, yaws, and sporotrichosis, as well as to the unique case of coccidioidomycosis reported earlier by Wilson, Smith, and Plunkett. Certain immunologic phenomena, to be discussed under that heading in later paragraphs, were considered to add credence to this view.

In these four cases the primary lesion appeared at the inoculation site within one week and was followed in about two weeks by lymphangitis and lymphadenopathy localized to the affected limb. In two cases, several tender nodules were noted along the lymphatic vessels, resembling the process seen in sporotrichosis but less severe.

Although the evidence is not conclusive, it appears possible that blastomycosis acquired in this manner has a tendency to be much milder than its other forms and perhaps to heal spontaneously. It must be admitted that the primary lesion was excised in three cases and the lymph nodes in the other, but in no case were both of these infected areas extirpated. No chemotherapy which could be considered "specific" in the least degree was employed. Nevertheless all the lesions entirely healed within four months without the chronic "localized cutaneous" form of the disease developing, and the patients remained well, one for 44 years and another for 27 years.

2. CHRONIC LOCALIZED CUTANEOUS BLASTOMYCOSIS.—In its commonest form, North American blastomycosis is first observed as a cutaneous lesion and remains apparently limited to the skin throughout a chronic course extending over many years, rarely spreading to other organs. These

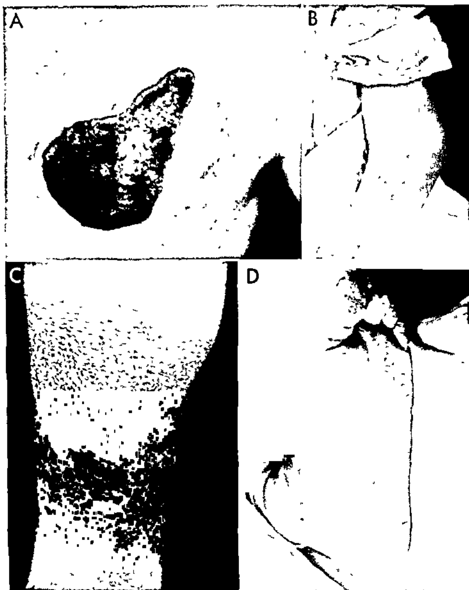


Fig 97 Blastomycosis **A**, irregularly-shaped, elevated plaque Slanting superior border is well shown Disease may secondarily involve bones and subcutaneous tissues **B**, elbow. **C**, leg **D**, ankle (**A**, *courtesy of Drs C F Lehmann and J L Pipkin*)

facts have been widely accepted as indicating that the fungus was inoculated directly into the skin at the site of the initial lesion. The preceding paragraphs cite evidence tending to refute this view, pointing out that all known inoculations of this sort have resulted in an entirely different clinical picture, an acute chancriform primary lesion accompanied by regional lymphangitis and lymphadenopathy and tending probably toward early spontaneous involution. In addition, Schwarz and Baum have succeeded in finding evidence of pulmonary or other systemic involvement in many cases which had appeared on less intensive examination to be of the classic chronic type limited to the skin. Thus, it now seems likely that this type of blastomycosis is but another of several forms which arise by dissemination from primary foci elsewhere, usually the lungs.

Regardless of arguments as to the mode of origin, localized cutaneous blastomycosis begins as an isolated papular lesion in or just beneath the skin or as a subcutaneous nodule developing into an abscess and eventually rupturing to form an ulcer. The lesion soon develops a verrucous appearance studded with tiny pustules, the whole being raised above the surrounding normal skin from 3 to 6 mm. It slowly extends peripherally and when a few centimeters in diameter begins to subside at the center, where it eventually tends to "burn out," leaving atrophic noncontractile scars. Other lesions may appear, and by irregular peripheral growth and coalescence, gyrate, arciform, and serpiginous forms are produced Typically, there is a characteristic verrucous ridge a few millimeters in height, with many pustules and exudative crusts on its crest, resting on a tumid violaceous base which terminates sharply and precipitously at the edge of the normal surrounding skin centrifugally and equally suddenly in scarred atrophy toward the center There is but little penetration into the skin, usually not more than 3 to 5 mm

Expansion typically continues for many years, the infection eventually covering surprisingly large areas of the body but having a strong tendency to remain roughly contiguous to its point of first appearance Thus one limb or one side of the trunk or face may be the only involved site throughout the entire course of the disease The process in general resembles a fire in a field of grass, islands of skin are frequently left uninvolved or islands of activity remain long after they have become separated from the main mass of the infection Recurrent infection in scarred areas occurs, in contrast to syphilis

3 PRIMARY PULMONARY BLASTOMYCOSIS —Although much evidence indicates that the lungs are frequently (if not indeed almost invariably) the portal of entry for blastomycosis, the ensuing disease is so insidious in its development that little is known of the primary phases At first, it apparently resembles an ordinary subacute respiratory infection, there being a nonproductive cough, moderate fever, chest pain, and dyspnea These symptoms gradually increase in severity, bloody and purulent sputum appears, and weakness, anorexia, and weight loss are prominent. The fever



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calcis

increases, and night sweats frequently occur. Pleurisy is occasionally observed. Erythema nodosum has recently been reported, its presence being reminiscent of its frequent accompanying of coccidioidomycosis in the same stage.

By physical examination it is difficult to differentiate pulmonary blastomycosis from massive tuberculosis or lung abscess unless the infection succeeds in eroding through the chest wall to form discharging sinuses in the skin. X rays may reveal marked enlargement of the mediastinal nodes, but this is frequently hidden by massive densities projecting irregularly from that area, in a manner strongly suggesting bronchogenic carcinoma. The pulmonary involvement may be unilateral at first but usually becomes bilateral. Cavitation is not common, and the lesions are usually small and irregular in outline. Evidence of massive miliary spread is sometimes seen.

4. Disseminated blastomycosis.—In addition to the specialized cutaneous form previously discussed, blastomycosis may be disseminated hematogenously to other parts of the body. The bones are involved in almost two-thirds of the cases, most frequently the ribs and vertebrae. X rays reveal such lesions to be both destructive and proliferative, resembling tuberculosis more than the cystlike appearance of coccidioidomycosis, but less proliferative than actinomycosis. Collapse of vertebral bodies may result in spinal cord compression.

The viscera are frequently invaded, especially the liver, spleen, prostate, and kidneys. Central nervous system lesions occur in about one-third of the cases The intestinal tract is usually spared, in striking contrast to the situation in South American blastomycosis.

There is usually leukocytosis, with an increase in polymorphonuclears, and a heightened sedimentation rate. Anemia of the hypochromic type is typical

PATHOLOGY

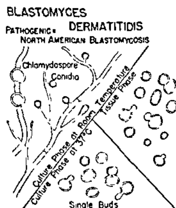
In primary cutaneous blastomycosis, the primary lesion is seen to consist of a dense infiltrate of lymphocytes and polymorphonuclear leukocytes within which are numerous budding cells of *B. dermatitidis*. Where it has not been destroyed by ulceration, the overlying epidermis shows only a slight acanthosis. The lymphangitic streak reveals an inflammatory infiltrate containing a multiplicity of cell types and numerous blastomycetes. The lymph nodes show foci of acute granulomatous lymphadenitis in which are many giant cells occasionally containing fungus organisms

In chronic localized cutaneous blastomycosis, the picture differs markedly from that of the primary form. The acanthosis is more marked than in any other disease, assuming to the highest degree the condition called pseudoepitheliomatous hyperplasia, frequently mistaken for squamous cell carcinoma There are numerous microabscesses, many of which are wholly intraepidermal, containing pus composed largely of polymorphonuclear

general acceptance, and it seems better to retain Blastomyces until more is known about its life cycle.

B. dermatitidis is biphasic, as are several other fungi capable of causing deep mycoses. In animal tissues it exists only as spherules, reproducing only by the production of buds, one at a time This phase alone is seen in artificial cultures if they are maintained entirely at temperatures simulating that of the bodies of animals (about 37 C.). At lower temperatures artificial culture produces none of these spherules, but a mycelium, bearing small pear-shaped conidia

1. Direct microscopic examination —This may reveal the organisms in pus from cutaneous lesions or draining sinuses. In sputum, pleural



exudate, or cerebrospinal fluid it is very difficult to differentiate them from artefacts

It is advantageous to prepare slides in two ways, as advocated for coccidioidomycosis For the first, a drop of the material is mixed on a slide with a drop of 10 per cent potassium hydroxide, a coverglass placed over the mixture, and this area heated gently from below, this procedure resulting in "clearing" in the usual manner Under reduced light intensity, the organisms appear as spherical bodies varying from 8 to 18 microns in diameter, with a thick refractile wall giving the so-called "double-contoured" appearance Some cells will be seen to be in the process of producing a single, thin-walled bud or daughter cell, arising by the extrusion of nuclear and cytoplasmic material through an opening in the cell wall. Typically there is a short curved neck between the parent cell and the bud, in contrast to the picture seen in the case of Coccidioides, where it is obvious that two spherical cells have simply been pressed together, forming a plane at the area of contact. This neck is shorter and wider than that usually seen in Cryptococcus neoformans

When the parasites are sparse or the examiner is not intimately famil-

leukocytes and some lymphocytes and only an occasional fungus cell. Giant cells are frequently present and sometimes contain the blastomycetes. When blastomycosis is suspected, the experienced histopathologist will request multiple, serial sections in which these intraepidermal microabscesses will be carefully examined first, since the rare blastomycetes are more easily found and identified there than elsewhere. Below the extremely irregular epidermis there is a dense infiltrate in which polymorphonuclear leukocytes predominate. Within this active mass there is almost no connective tissue stroma, but many dilated blood vessels are present. Fungus cells are found here but rarely. In sections taken from areas in which the disease is subsiding, fibrosis is present, but it is usually not firm or dense.

Pulmonary blastomycosis may grossly resemble carcinoma or at times tuberculosis. There are seen nodules of all sizes, some of which are caseous, abscesses, and occasionally cavitations. Pleural thickening is common, and frequently the disease extends beyond the pleura to involve the ribs and sometimes even to penetrate the chest wall and discharge externally.

Involvement of the lungs is practically always present in persons dying of blastomycosis. In this event the organisms are usually present in large numbers, with a comparatively slight cellular inflammatory reaction.

Disseminated blastomycosis involves many organs, and the resulting lesions contain more numerous organisms as the disease progresses and the efforts of the tissues to combat it become lessened. In the earlier stages there is pyemia, later, tubercles, necrotic zones, and abscesses appear. Bony lesions are common, frequently resulting in subcutaneous abscesses or sinuses draining through the skin Muscles may contain focal lesions; even psoas abscess as seen in tuberculosis has been reported. Pericarditis occurs, sometimes causing death by effusion. Abscesses appear in lymph nodes, spleen, liver, kidneys, prostate, fallopian tubes, and uterus. Meningitis or brain abscesses are not rare. In autopsy material the organisms may be present in such large numbers as to appear almost as though in pure culture, the body of the host having long since ceased to offer much immunologic or cellular resistance This picture is in striking contrast to that seen in the chronic cutaneous form, in which such resistance is very high

MYCOLOGY

North American blastomycosis is caused by a single species of fungus, the most widely accepted botanical name for which is Blastomyces dermatitidis Strict adherence to the rules of botanical nomenclature would necessitate using some other term than Blastomyces, since it had previously been given to an entirely different fungus Also, the phenomenon of budding, which the first root designates, is observed only in the tissue phase of B dermatitidis, while it is exhibited more constantly and typically by many other fungi, even being the sole form of reproduction of some. However, none of several attempts to classify this organism differently have gained



Fig 99 Blastomyces dermatitidis. A, histologic section, showing granulomatous changes with multiple abscesses, × 150 B, infiltrate from section composed mainly of

iar with this fungus, it may be impossible to differentiate the organisms from globular artefacts or other cells. Slides prepared by the second method are extremely useful here. A drop of exudate should be diluted with a drop of normal saline solution and placed beneath a coverslip, the under edges of which have been coated with petrolatum by being drawn across the thenar eminence of the palm, which has been coated with this substance Specimens prepared in this manner will not dry out for several days at room temperature, and within 24 hours viable Blastomyces spherules will begin to "sprout," each sending out a single hyphal thread. (Compare with Coccidioides, each spherule of which produces several strands.) This method often yields a reliable diagnosis long before histopathologic preparations or culture do so.

In sections of animal tissues, the spherules and budding cells appear as described in the preceding paragraphs. Hematoxylin colors the walls poorly, while the nuclear material becomes deep blue and is seen to occupy more than half of the cell. The periodic acid-Schiff stain (Hotchkiss-McManus) reveals the detail very well and by its differential staining serves admirably to call attention to cells so sparsely present as to be otherwise easily missed. In sections of skin, organisms are more easily found in serial sections through the intraepidermal abscesses and in giant cells than elsewhere.

2 CULTURAL CHARACTERISTICS.—Although it grows well when subcultured, B dermatitidis is frequently among the most difficult of fungi to isolate from infected tissues or exudates This is due in part to the paucity of organisms typical of many cases, especially of the chronic cutaneous form, as well as to the presence usually of myriads of secondary bacteria. It is well to inoculate several plates each of two sorts, one containing blood or beef infusion agar and the other Sabouraud's glucose agar, specimens of both types should be held at 37 C. as well as at room temperature The inclusion in the medium of substances to inhibit the growth of bacteria is advantageous.

At incubator temperature the fungus grows slowly and develops white or cream-colored, waxy, yeastlike or bacteria-like colonies, becoming wrinkled with age Microscopic examination reveals the spherules and budding cells previously described and in addition a few cells which are abortively attempting to form hyphae, represented by short stems

At room temperature, the colonies are yeastlike and waxy at first, resembling Geotrichum grossly, but soon develop a white aerial woolly mat indistinguishable from colonies of many other fungi. Occasionally, however, coremia are formed, consisting of twisted strands, each composed of many hyphal threads, giving the colony grossly the appearance of a prickly pear or cactus While other fungi may produce this phenomenon, its appearance from inoculation of material from clinically suspicious lesions strongly suggests B dermatitidis Microscopic examination of portions of the aerial mycelium reveals many conidia, 3 to 5 microns in diameter, oval,

dissemination from a previously unrecognized primary pulmonary infection. In this case, the lungs and other organs apparently succeed in resisting the disease, while the skin fails, although it tries hard and almost succeeds. This concept is in keeping with the histopathology of such cutaneous lesions, which is seen to represent a strenuous effort to resist a very small number of blastomycetes by producing a tremendous cellular infiltrate and pseudoepitheliomatous hyperplasia.

In contrast, in all four instances of known percutaneous inoculation of blastomycetes there was complete recovery. In those cases in which such tests were employed the skin reacted well, while there was no reaction to the complement fixation test. There is as yet no information indicating that blastomycosis exists in a widespread benign form, as is known to be the case with coccidioidomycosis and almost certainly with histoplasmosis, but it must still be considered possible A significant number of "normal" persons living in the vicinity of the small epidemic reported from North Carolina were found to react positively to the skin test, a reaction indicating the likelihood of a previous "benign" unrecognized infection (Smith, Harris, Conant, and Smith).

DIFFERENTIAL DIAGNOSIS

Primary cutaneous blastomycosis must be differentiated from the chancriform stages of the other infectious granulomata, particularly tuberculosis, syphilis, and sporotrichosis. The chronic localized cutaneous form must be differentiated from tuberculosis verrucosa cutis, bromoderma, iododerma, and granuloma inguinale. The pulmonary infection may simulate neoplasm, tuberculosis, or other deep mycoses The disseminated form must be differentiated from many diseases, especially tuberculosis, neoplasms, syphilis, and other deep mycoses.

PROGNOSIS

Except for the primary cutaneous form, in the four known cases of which there was recovery, blastomycosis must always be considered a serious disease. As far as our present knowledge goes, pulmonary blastomycosis usually becomes disseminated This type is often fatal, but in some cases all disseminated lesions heal except those in the skin, the condition then being known as the chronic localized cutaneous form, which seldom kills the patient but may persist for many years

Information elicited by the use of blastomycin in the intracutaneous test and determination of the complement fixation titer are of great prognostic value Patients exhibiting a high antibody titer by the complement fixation test and low reactivity to the skin test will probably die of the infection. The outlook is entirely different for those reacting well to the skin test while the serum does not fix complement with blastomycin.

pear shaped or spherical, each borne singly on a short conidiophore or directly from the side of a hypha. Some strains may be converted from this mycelial phase to the yeastlike form by placing subcultures in the incubator immediately; others require passage into animals and culturing immediately at 37 C. from the infected tissues.

3. ANIMAL INOCULATION.—Intraperitoneal injection of infectious material or suspected culture fragments into guinea pigs or mice yields typical lesions in the liver, spleen, lungs, and lymph nodes. These areas frequently contain the organisms in much larger numbers than were present in the original material, and it is then much easier to identify them by direct examination or histopathologic study.

IMMUNOLOGY

It has long been known that an extract of cultures of B. dermatitidis (called blastomycin, and analogous to tuberculin and coccidioidin) could fix complement in conjunction with the sera of persons suffering from extensive blastomycosis In many of the milder cases of the localized chronic cutaneous form, however, no reaction occurs Blastomycin also may be used intracutaneously and in many instances yields positive reactions of the delayed tuberculin type, even when diluted 1:100. These phenomena are reasonably specific, although there is some cross reaction, especially with histoplasmin and in histoplasmosis It is likely that a higher degree of specificity can be attained by better standardization of material, by using higher dilutions, and by acquiring more experience

As early as 15 years ago Martin called attention to the fact that persons whose sera were able to fix complement with blastomycin in fairly high dilutions (1 32) usually succumbed to the disease, while those whose sera were only slightly reactive or failed to react recovered; also, that ability to react to the intracutaneous blastomycin test was a sign of a good prognosis, while patients who died usually had lacked this reactivity Although by no means as clearly defined, these are the exact counterpart of observations made by many clinicians in coccidioidomycosis. It must again be emphasized that there is insufficient evidence for a conclusion that immunologic resistance is intimately concerned with the substances responsible for these reactions, the clinician may nevertheless utilize them as valuable aids in prognosis

It has been difficult to explain why many patients exhibiting chronic cutaneous lesions over a period of years failed completely to react to the complement fixation test or did so only with low dilutions, while their skin test reactivity was frequently high

It is possible that some of the discrepancies may be resolved by the concept advocated by Schwarz and Baum and amplified by Wilson, Cawley, Weidman, and Gilmer that the usual chronic cutaneous form of blastomycosis does not result from primary percutaneous inoculation but represents

cultures of B. dermatitidis in its yeastlike phase is recommended as stimulating the development of immune bodies. It is considered dangerous by some authorities to administer iodides to patients exhibiting a high reactivity to the intracutaneous test with blastomycin until considerable desensitization has been accomplished. Further details of these procedures may be obtained from the writings of Martin and Conant *et al.*

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TREATMENT

The treatment of North American blastomycosis has always presented many discouraging features. Potassium iodide to the point of tolerance has been employed both orally and parenterally in most cases, with benefit in many and failure in others. The same can be said of X radiation, surgical intervention, and vaccinotherapy. Recently, the outlook has improved considerably through the discovery by Elson that certain derivatives of stilbene exert an apparently specific chemotherapeutic action on this disease. A large number of similar compounds, most of which contain the double-bonded carbon of ethylene (styrene, nitrostyrene, cinnamic acid, etc.), are being investigated by Curtis *et al.*, and some appear promising. Stilbamidine is as yet the most widely used of these drugs and is administered in a dosage of 150 mg daily for two weeks, given slowly intravenously in 500 cc. of normal saline, followed by a second similar course after an interval of two weeks. Neurotoxicity has been troublesome, especially with regard to the trigeminal nerve, and hepatotoxicity has been encountered in serious degrees. Hydroxystilbamidine is reported to be less toxic. The clinical response is much better in the chronic cutaneous type than in the pulmonary or disseminated forms. This type of chemotherapy is in a state of flux at the time of this writing, and more recent publications should be sought before treatment is begun.

Not enough is known about the rare primary cutaneous form to furnish a guide to therapy In all four known cases, some degree of surgical intervention was employed, but in no case was all of the infected tissue removed Nevertheless all patients recovered completely.

In the localized chronic cutaneous form, the diseased areas may be healed by thorough curettage and desiccation, a procedure which is accomplished with surprising ease, since all involved tissue separates without resistance from an apparently comparatively healthy base. Subsequent use of Lugol's compound solution of iodine diluted equally with water as a daily dressing usually results in healing by scarring Recurrences are fairly common but usually yield to subsequent retreatment while still small. Attempts to remove large areas of involved skin surgically followed by full thickness grafts have been less successful The recent concept that this form of the disease really represents the end stage of a process of dissemination in which all body tissues except the skin have acquired sufficient resistance against it removes to a large extent the reluctance to attack such lesions surgically because of fear of disseminating the organisms

In the pulmonary and disseminated forms particularly, it is necessary to employ all those measures which are calculated to enhance the development of immunologic resistance, such as prolonged rest in bed, a high caloric and high protein diet, supplemental vitamins especially B and C, crude liver extract, and transfusions of whole blood. Steroid hormones are probably harmful (Friedman *et al*) A heat-killed vaccine prepared from

30. South American Blastomycosis

(Paracoccidioidomycosis)*

SOUTH American blastomycosis is a chronic, progressive, usually fatal granulomatous disease concentrated in the mucous membranes, lungs, lymph nodes, skin, and viscera, caused by a single species of fungus called by various names, the commonest of which is Blastomyces (or Paracoccidioides) brasiliensis. Although the infection occurs in only a small portion of the world, the facts concerning its pathogenesis are worthy of study by practitioners in other regions as well, lest the search for methods of control of the medical mycoses in general be hampered by lack of information concerning some feature less elusive in this entity than in others In addition, in two instances the diagnosis has been made outside of South America, although in both it seems likely that the disease was acquired there (Chavarria *et al.* and Perry, Weed, and Kierland)

HISTORY

In 1908, Lutz in São Paulo, Brazil, observed two patients with lesions of the oral mucosa accompanied by cervial lymphadenopathy. He isolated the causative fungus, described its multiplication by a budding process, and named the disease "pseudococcidioidal granuloma" There soon followed other reports, by Carini and by Splendore, concerning the clinical aspects of the disease and confirming Lutz's observations on the morphology of the fungus.

In subsequent years numerous papers appeared in the literature, usually suggesting new designations for the fungus and sometimes indicating

* This chapter was written in collaboration with Dr Tancredo A Furtado, of Belo Horizonte, Brazil, whose assistance is gratefully acknowledged

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that South American Blastomycosis was being confused with coccidioidomycosis.

Beginning in 1929, Almeida presented a series of papers concerning the mycology, pathology, and symptomatology. More recently, Bogliolo and Aroeira Neves carefully studied the morphology and taxonomy of the causative fungus, presenting several new observations.

ETIOLOGY

Although there has been much disagreement as to the naming of the causative organism, it is generally accepted that there is but one species of fungus involved in South American blastomycosis.

DISTRIBUTION

South American blastomycosis has been reported only from that continent, principally in the Brazilian states of São Paulo, Rio de Janeiro, and Minas Gerais and in Argentina.

The incidence of the disease is highest at the ages from 20 to 50, and males outnumber females six to one. There is a remarkably high incidence among agricultural workers, presumably because they come into more direct contact with vegetative material.

EPIDEMIOLOGY

The habitat of the causative organisms in nature has not yet been established The clinical aspects of the disease indicate strongly that the portal of entry is usually the oral mucosa, and the prevalence of the infection among agricultural workers is generally accepted as being due to their habit of cleaning the teeth with small fragments of wood and chewing the stems and leaves of various plants. Although attempts to prove the existence of the fungus on such material by artificial culture methods have not been successful, it appears almost certain that the infection is acquired from such an exogenous source It must be recalled, however, that a similar mechanism was long accepted for the acquisition of actinomycosis due to *A bovis*, which later evidence has shown to be endogenously acquired

Direct transmission from man to man or from animals to man has not been proved The reasons for the sharp limitation of the disease to the continent of South America are not clear

CLINICAL CHARACTERISTICS

The primary lesion of South American blastomycosis almost always occurs in the mucous membrane of the gastrointestinal tract, usually that of the mouth and occasionally that of the tonsils, larynx, nose, eye, intes-



Fig 101 South American blastomycosis. Lesions are characteristically on face and have often a striking resemblance to North American blastomycosis In D is shown variety known as keloidal blastomycosis (*A and D, courtesy of Prof Carlos da Silva Lacaz, B, courtesy of Dr Tancredo A Furtado, and C, courtesy of Prof Aguiar Pupo*)

tine, or anus. Rarely, the lungs appear to be the primary site. Primary inoculation into the skin is apparently rare, and convincing evidence is difficult to obtain.

From any of these primary foci, the infection may be disseminated by both the lymphatic and the hematogenous route and may affect practically all organs eventually.

In a recent report, Azulay pointed out that the disease seldom remains sufficiently limited to any one organ system to allow it to be classified into various types. For clarity in description he favored separation according to clinical manifestations into "tegumentary" and "extrategumentary" forms of involvement. The term tegumentary includes mucosal as well as cutaneous lesions.

1. Tegumentary clinical manifestations.—The primary lesions are found most often on the mucosal surface of the gums, cheeks, lips, palate, nose, and tongue They are usually erythematous, ulcerated areas showing characteristic tiny, yellowish spots interspersed with reddish ones, giving a fine granular appearance. This picture was described by Pupo, who named it "mulberry-like erosive stomatitis." Occasionally the lips become swollen sufficiently to justify the descriptive term "proboscis-like lip."

Cutaneous lesions may occur on the skin around the mouth or nose in continuity with the involved mucosa. The skin becomes affected secondarily by ulceration and fistulization of enlarged lymph nodes, particularly in the cervical region, simulating scrofuloderma. Cutaneous lesions are frequently hematogenous. They may be papular, papulopustular, papulotuberous, papillomatous, frambesiform, ulcerated, and ulcerovegetative. They may occur in large numbers, usually on the face but also on the trunk and extremities The subcutaneous tissues may be invaded by the extension of mucosal or cutaneous lesions or by the hematogenous route.

Jorge Lobo first observed and described a cutaneous keloidal type, especially involving the back and legs, which bears no resemblance to the usual clinical picture of the disease. Seven cases have been studied, some observers concluding that the syndrome is only an unusual form of South American blastomycosis caused by the same species of fungus but more actively resisted by the patient (Almeida, Area Leão, Furtado, Lisboa), while others believe both the disease and the organism to be different, the latter termed Paracoccidioides loboi (Lobo, Lacaz, Bogliolo).

2. Extrategumentary clinical manifestations —(*a*) *Lymph nodes* —Involvement of the lymph nodes, sooner or later in the disease, is one of the commonest features of South American blastomycosis The cervical and the submaxillary groups are most commonly affected, becoming involved from lesions in the oral mucosa or in the tonsils Sometimes the presence of enlarged lymph nodes is the only apparent clinical manifestation of the mycosis The lymphadenopathy may be sufficiently generalized to simulate Hodgkin's disease Eventually the nodes suppurate and rupture through the skin.

2. HISTOPATHOLOGY.—Biopsy shows the histopathologic changes to be those found in a [illegible] be assured only by the finding ([illegible] he tuberculoid or of the foreig [illegible] ulceration, microabscesses, and epithelial hyperplasia, sometimes simulating carcinoma. Abscess formation may occur in the reticular corium, in which neutrophils predominate, but lymphocytes, plasma cells, and a few eosinophils may also be found. The fungus may appear in the interior of the giant cells, in the abscesses, in the microabscesses, or elsewhere in the corium or in the epidermis.

The finding of a tuberculoid reaction does not indicate that the organism is absent in the lesions In fact, nonspecific acute inflammatory and tuberculoid or foreign body reactions have been demonstrated side by side in the same section, a situation similar to the picture seen in coccidioidomycosis.

The fungus appears in two different forms, producing buds either singly or in multiples. The latter is the commoner type and consists of a thick-walled parent cell 10 to 60 microns in diameter, with buds appearing only at a few points or studding the entire surface. Transverse sections through one of these larger cells shows the picture which is the most characteristic for this fungus, with buds around the periphery, the whole vaguely resembling a marine pilot's wheel. The buds may be as small as 1 to 2 microns in diameter, simulating cocci, or as large as 10 microns They are usually round but may be oval, ellipsoid or pyriform They usually become separated from the parent cell while still very small, in contrast to B dermatitidis. Less commonly, singly budding forms are seen, 6 to 20 microns in diameter and very similar to those produced by B. dermatitidis. The multiple-budding forms are usually seen in the lymph glands or the spleen and are rare in epithelial lesions, in the latter it is often difficult to differentiate the predominantly singly budding forms from B. dermatitidis.

In sections stained with hematoxylin and eosin the cytoplasm is usually basophilic and may show small vacuoles. The Hotchkiss-McManus stain reveals the structure more clearly.

MYCOLOGY

Most investigators agree that a single species of fungus is the causative agent of South American blastomycosis, but there is as yet no agreement as to its exact taxonomic position The suggestion by Conant and Howell that because of its similarity to the fungus causing North American blastomycosis it should be placed in the same genus, Blastomyces, has not been widely accepted in South America, where other generic names, Paracoccidioides, Lutziomyces, and, most recently, Aleurisma are preferred The species name is usually brasiliensis, although histo-poro-cellularis was long used

Blastomyces (Paracoccidioides) brasiliensis is strictly biphasic in its

(*b*) *Respiratory system*.—Until recently pulmonary involvement in South American blastomycosis was considered to be so rare as to furnish a means of clinical differentiation between that mycosis and North American blastomycosis (Gilchrist's disease). Many authors have shown, however, that the lungs are affected in a high percentage of cases (57 per cent to 94 per cent). The clinical signs show wide variations. The patient may or may not have a cough with purulent sputum, which is occasionally blood streaked. Râles may be audible. However, the signs and symptoms are often mild, contrasting with the severity of the parenchymatous changes revealed by X-ray studies or at autopsy. The roentgenographic aspects include macronodular and micronodular lesions, disseminated or grouped miliary lesions, fibrosis, occasional small cavities, and pleural thickening. Lesions tend to be bilateral and localized near the bases or in lines spreading fanwise from the hilus, which is itself usually free. The pulmonary picture is by no means diagnostic and should always be differentiated from tuberculosis, which is frequently associated. Lesions in the larynx may produce dysphonia or aphonia.

(*c*) *Digestive tract*.—The mouth and pharynx are affected in almost every case, the gastrointestinal tract, less frequently and usually only secondarily to other manifestations of the disease. It may happen, however, that the gastrointestinal process is the primary one and remains the only manifestation. In such a case, because of the lack of specificity of the symptoms, the diagnosis is made only at autopsy.

Appendical lesions have been studied by several authors. Involvement of the anorectal region has been reported.

(*d*) *Other organs*.—The spleen and liver may be enlarged. Peritoneal localization has been reported. Involvement of many other organs has been observed occasionally, producing highly variable clinical pictures.

PATHOLOGY

The macroscopic and microscopic changes in the tissues are not specific and are similar to those found in other deep mycoses, most closely resembling those in North American blastomycosis.

1. Gross pathology.—The predilection of the fungus for the lungs is a remarkable fact. Contrary to the work of former investigators, who reported infrequent pulmonary involvement, Fialho found it in 84 per cent of the 25 patients he autopsied. Nodules, cavitary lesions, and abscesses are found. Some nodular lesions may undergo regressive changes and calcification. The lymphatic tissue is usually affected. Gummatous lesions, necrosis, necrobiosis, and fibrosis are common. Lesions are common in the digestive tract, especially the mouth, the pharynx, and the portion from the jejunum to the anus. In the latter segment, round ulcers, formed consequent to previous ulceration in the underlying lymphoid tissue, may become confluent and form large ragged ulcerated areas. Involvement of the skeletal system is not as rare as previously believed.

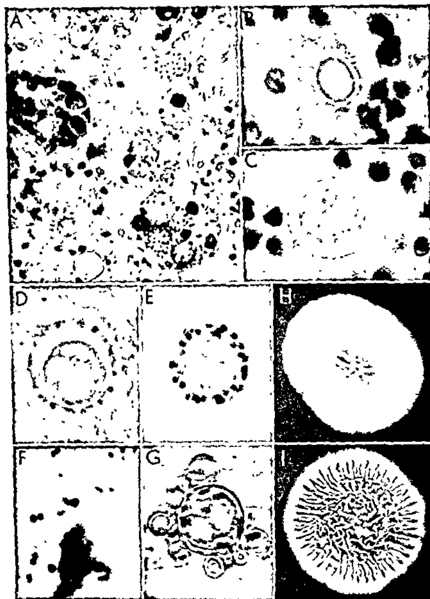
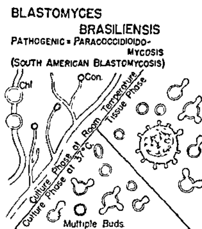


Fig 102. Blastomyces (Paracoccidioides) brasiliensis A, different phases of life cycle,

Floriano de Almeida)

life cycle, as are so many others among the organisms capable of causing deep mycosis. In animal tissues reproduction is carried out only by the production of single or multiple buds, as described in the discussion on histopathology. This form is maintained usually in artificial cultures carried out at 37 C. At lower temperatures, a filamentous phase is the only form encountered.

1. Direct microscopic examination.—Material obtained from lesions consisting of pus, exudate, or crushed bits of tissue should be examined directly or after being warmed with potassium hydroxide solution. The characteristic multiple or singly budding forms may be seen.



2 Cultural characteristics —Infected material or exudate should be inoculated into both blood agar and Sabouraud's glucose agar and maintained at both incubator temperature (37 C.) and room temperature. Growth begins very slowly on primary isolation, appearing usually within 20 days but sometimes much later Subcultures grow more rapidly.

At 37 C. the gross appearance of the colony is that of a smooth or cerebriform, white or tan, greasy paste. Microscopic examination of this material reveals cells producing single or multiple buds, as previously described Often long chains of buds are formed, either branched or unbranched.

At room temperature, the colonies are white or yellowish, wrinkled, and firm and present fluffy aerial mycelia Older colonies become brown Microscopic examination of fragments of such colonies reveal mycelial threads, branched and septate, with intercalary or terminal chlamydospores. Structures closely resembling the conidia of B dermatitidis have been described Recently, Aroeira Neves and Bogliolo studied this phase of the fungus and described certain pyriform flattened or quadrangular spores, which they termed "aleurospores," appearing laterally along the hyphae with or without a pedicle, and which later remain attached to the dead empty hyphae, in contrast to true conidia On this basis they suggested

THERAPY

Iodides, gold and antimony salts, and antiseptic dyes are considered valueless. Sometimes localized lesions may be successfully destroyed by electrocoagulation. Almeida reported good results with specific vaccines.

Sulfadiazine is the drug most extensively used in practice, fractionally administered in a total dose of 2 to 4 Gm. daily. Clinical improvement may be expected in most patients, and clinical cure, occasionally. Relapses are frequent when the drug is discontinued, and sufficiently prolonged administration may be prevented by toxic manifestations. As with the other deep mycoses, a diet high in protein content and those vitamins which are related to immunity development (vitamins B and C) should be maintained.

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that the correct generic name for the organism is "Aleurisma." Almeida and Conant said they believed the evidence to be insufficient.

3. ANIMAL INOCULATION.—Intraperitoneal inoculation of the yeast-like form into mice has produced nodules rich in parasites in the mesentery, liver, spleen, and diaphragm. Generally, however, the lesions tended to involute rather than to progress. Intratesticular inoculation of guinea pigs, producing an orchiepididymitis which usually remains localized, is preferred by some

IMMUNOLOGY

There seems to be little attempt on the part of the human body to resist the progress of South American blastomycosis by specific immunologic processes.

1. INTRACUTANEOUS TEST.—The intradermal injection of antigens prepared from cultures of the organism or from pus has not yielded uniform results in the hands of different investigators. Almeida, Lacaz, and Cunha consider the test of value in both diagnosis and prognosis In the severe forms of the disease the reaction is negative. The test does not seem highly specific with the present antigens.

2. COMPLEMENT FIXATION REACTION.—The standardization of this reaction has not yet been achieved, and its significance is not known. There are indications, however, that a high titer indicates a poor prognosis and that recovery may be heralded by a decreasing titer (Lacaz and Fava Netto). (*See* Chapters 29, 31, and 32, on North American blastomycosis, histoplasmosis, and coccidioidomycosis, respectively.)

DIFFERENTIAL DIAGNOSIS

South American blastomycosis is a markedly polymorphic disease and must be differentiated from a large number of clinical entities Lymphadenopathy being a prominent feature, scrofuloderma and Hodgkin's disease should be considered primarily and then other deep mycoses, such as North American blastomycosis, coccidioidomycosis, actinomycosis, histoplasmosis, cryptococcosis, and sporotrichosis Leishmaniasis, yaws, syphilis, certain neoplasms, and aleukemic leukemia should be borne in mind. In cases presenting initial lesions limited to the oral mucosa, certain manifestations of vitamin B complex deficiency, aphthous stomatitis, periadenitis mucosa necrotica recurrens (Sutton), and Vincent's stomatitis should be considered.

PROGNOSIS

Before the introduction of the sulfonamides, South American blastomycosis was usually fatal Recently life expectancy has been highly improved, and a few clinical cures have been reported

31. Histoplasmosis

(Reticuloendothelial Cytomycosis)

THE fungus Histoplasma capsulatum causes histoplasmosis, usually described as a rare, chronic, fatal, granulomatous disease with a distinct predilection for the reticuloendothelial system. During recent years, however, increasing evidence indicates the probability that in certain geographic areas the infection, instead of being rare, occurs very frequently, in the form of a pulmonary infection so mild as to result almost uniformly in recovery and subsequent immunity. All practitioners of medicine should, therefore, become familiar with the essential facts concerning its diagnosis so that it will be less frequently missed. Statistical studies may then clarify its epidemiology, pathogenesis, and immunology.

HISTORY

Histoplasmosis was first delineated by Darling in 1906 while he was searching for leishmaniasis in the Panama Canal Zone He believed the causative organism to be a protozoan and named it Histoplasma capsulatum Da Rocha Lima proved the organism to be a fungus in 1912. De Monbreun, Conant, and Howell have studied its life cycle. Palmer in 1945 and Peterson and Christie suggested that pulmonary calcification in nontuberculous persons may frequently be attributable to a mild pulmonary form of histoplasmosis previously unrecognized Recently, many investigators have become interested, and it is to be expected that further important chapters in the history of histoplasmosis will soon be written

ETIOLOGY

Histoplasmosis is caused by a single species of fungus, Histoplasma capsulatum Although this name was given to the organism by Darling while he still believed it to be a protozoan, it has persisted The future may well bring alterations to each component of the name; Hansman and

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almost invariably acquired. Grayston and Furcolow analyzed 13 epidemics of various sizes and were impressed by the relationship with animal excreta, principally from chickens or pigeons, in dusty closed environments.

CLINICAL CHARACTERISTICS

Although the proof cannot yet be said to be conclusive, it is virtually certain that histoplasmosis occurs in two widely divergent forms, a mild primary infection affecting a large percentage of exposed persons and a severe disseminated type encountered only rarely There is apparently a close resemblance to coccidioidomycosis, especially with regard to epidemiology and immunity, although the two diseases differ extensively in their pathology.

1. PRIMARY PULMONARY HISTOPLASMOSIS.—The exact status of this entity has not been conclusively established A brief résumé of the evidence for its existence is as follows.

It has long been known that many persons exhibit roentgenologic evidence of pulmonary calcification which cannot be attributed to tuberculosis or any other disease heretofore delineated. The incidence of this phenomenon increases with advancing age from childhood to early adult life and is higher in certain geographic regions in a manner highly suggestive of its being due to some environmental cause. The discovery that it could be statistically correlated with reactivity to the intracutaneous injection of a substance known as "histoplasmin," analogous to tuberculin and coccidioidin, makes it appear likely that it is frequently the result of infection with H. capsulatum It is only necessary to accept the view that the active phase of the disease can frequently be so mild as to be asymptomatic or, when more severe, is incorrectly attributed to "the common cold," "influenza," tuberculosis, bronchopneumonia, or other entities. The situation seems to be identical with that which has been thoroughly established in coccidioidomycosis, and to students of the latter disease further evidence appears to be unnecessary

Conclusive proof must await opportunity for thorough examination of large numbers of young persons with mild pulmonary infections within the geographic areas tentatively designated as "endemic foci" As in coccidioidomycosis, the mild forms so necessary for study do not yield autopsy material, but deaths from unrelated causes, such as traumatic accidents, will eventually furnish alerted pathologists with invaluable opportunities to clarify many aspects If the use of cultural procedures adapted to fungi can be extensively popularized in the treatment of pulmonary infections, it may be possible to prove the presence of H capsulatum in sputum with significant frequency The simplest method, however, would be to demonstrate consistently conversion of the reaction to the intracutaneous histoplasmin test from negative to positive during the early phases of such pulmonary ailments in large numbers of persons This work has only begun

Schenken pointed out that this organism might be appropriately placed in the previously well-established genus Sepedonium, and recent innovations in staining procedures suggest that there is actually no capsule. It is advisable, however, to retain the familiar term until the necessity for change is thoroughly established.

DISTRIBUTION

Histoplasmosis occurs most frequently in North America, concentrating in the region of the Mississippi River Valley. A significant number of cases have been recognized in South America, Central America, Australia, Indonesia, the Pacific Islands, and South Africa and solitary examples in several European countries Greater awareness of the disease may bring additional cases to light to confirm the world-wide distribution which seems indicated.

The infection occurs at all ages, but the incidence appears higher in the very young and the very old, especially with regard to the fatal form Males greatly predominate except in childhood, when the trend is much less pronounced. The influence of occupation, so impressive in other deep mycoses, seems relatively unimportant here, although persons whose work brings them into intimate contact with the soil appear more likely to become infected.

EPIDEMIOLOGY

Emmons first demonstrated the presence of H. capsulatum in soil in 1949, confirmation was soon added by several observers. The distribution of the organism in nature may be limited by the fact that it needs high humidity, a restricted range of temperature, and acid soil for proliferation. Wilkerson considered the lime and other mineral contents of the soil important. Dogs, cats, rats, mice, cattle, skunks, ferrets, and a horse have been shown to have been infected by natural means, but there has been no proved instance of an animal's transmitting the disease to man. Direct transmission from man to man also has not been observed, although its possibility cannot be excluded Infected animals as well as human beings are known to excrete the fungus in sputum, feces, and urine.

The principal portals of entry for the infection are apparently the respiratory and gastrointestinal tracts, although "primary" cutaneous and mucosal lesions have been described Experimentally, animals have been infected by all of these routes The exact manner in which the fungus is brought to the body is in doubt, soil carried to the mouth on food or other objects seems a likely source, perhaps accounting for the frequency of the infection in early childhood and the frequency of oral lesions. There is mounting evidence, however, that the principal route may be inhalation of the organisms with air-borne dust in the manner in which coccidioidomycosis is

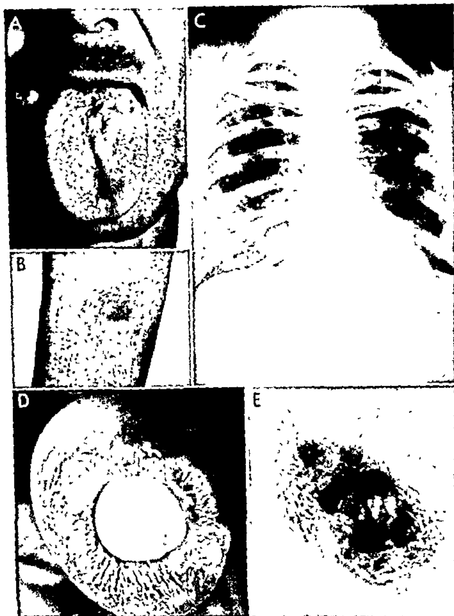


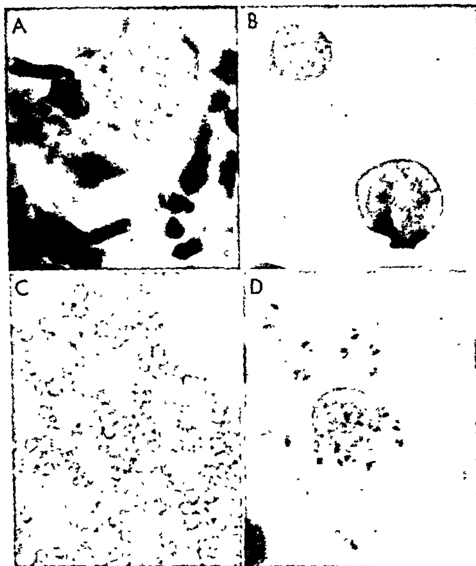
Fig 103 Histoplasmosis. A, infiltrated plaque on dorsum of tongue B, positive reaction after 48 hours to histoplasmin C, roentgenologic evidence of infection. D, lesion on penis E, ulcerating granuloma (A, *from Miller, Keddie, Johnstone, and Bostwick, Arch Dermat & Syph* 56 715, 1947)

Partly because of the known facts concerning coccidioidomycosis, it is assumed that spores of H. capsulatum are inhaled with dust. Cozad and Furcolow have shown that spores from cultures are small enough (less than 5 microns) to reach the pulmonary alveoli when inhaled. The subsequent course has been clarified by the observations of Furcolow, Gunteroth, and Willis and by Nilzen and Paldrok in mycologic laboratories in which several persons working with H. capsulatum sustained febrile pulmonary illnesses and thereafter reacted positively to the histoplasmin test. The incubation period was about two weeks. The illness began suddenly with fever, chills, dry cough, rhinitis, malaise, and generalized muscular pains. Most cases were mild and recovery ensued in less than a week. Roentgenograms revealed lesions suggesting bronchopneumonia, usually in the bases of the lungs, occasionally pleural effusion was evident. In one case, the illness lasted for five months, exhibiting a diffuse localized density in one lower lobe and hilar lymphadenopathy. Calcification was not observed in any case. H. capsulatum could not be identified either by culture or in material removed by bronchoscopic means. However, of a group of workmen studied by Loosli *et al*, who sustained a similar pulmonary ailment after clearing a silo, one yielded H. capsulatum from sputum and bone marrow specimens, the fungus was also cultured from material obtained from the silo

2 EXTRAPULMONARY PRIMARY HISTOPLASMOSIS.—The existence of this type of infection is much more doubtful than that of the pulmonary form Although initial lesions have been observed in the mucosa and skin, there is no conclusive proof that these sites were portals of entry, since the hematogenous dissemination which is known to occur could also explain this phase of the disease (*See* discussion on coccidioidomycosis, p 336) The disease has been produced, however, in animals by direct inoculation into the mucosa or skin, and similar infection of human beings must be considered possible.

3 DISSEMINATED, GRANULOMATOUS HISTOPLASMOSIS.—Although apparently much rarer than the primary types just described, the disseminated granulomatous form was the first recognized and accurately delineated. About 150 cases have been recorded Although the theory has not been proved, it is likely that disseminated cases simply represent those few instances in which persons afflicted with the primary form fail to resist the disease immunologically in the usual manner, as is the case in coccidioidomycosis In partial confirmation it may be pointed out that no alternative mechanism has been plausibly demonstrated in almost 50 years of study, although Grayston and Furcolow's studies seem to indicate that prolongation of contact with the infectious environment causes an increase in the severity of the symptoms

The reticuloendothelial system is particularly vulnerable to invasion by H. capsulatum Radaelli and Ciferri have shown that elements of the fungus introduced into animals are phagocytized by monocytes and macro-


A
B
C
D

[illegible]

phages, in which they do not die but multiply, and are subsequently borne hematogenously or by way of the lymphatics to organs rich in reticuloendothelial elements, such as the lymph nodes, spleen, liver, and bone marrow. Eventually, almost any tissue in the body except the cortex of bone or cartilage may become involved.

There is much variation in the rate of progress of the disease, and the clinical picture is protean. It is usually that of a subacute to chronic wasting, irregularly febrile disease, accompanied by anemia, leukopenia, lymphadenopathy, and enlargement of the spleen and liver. Anorexia, nausea, vomiting, diarrhea, and gastrointestinal discomfort may be prominent symptoms; pleurisy, pulmonary infiltration, and tracheobronchitis are frequently in evidence, endocarditis, involvement of the adrenals, or central nervous system invasion may occur. Mucosal lesions are often present, involving especially the genitalia and the mouth and tongue, these are usually torpid ulcers surrounded by induration Similar ulcers may occur in the skin, and purpuric or bullous eruptions are occasionally seen. X rays may serve diagnostically by revealing evidence of miliary spread, consolidations or hilar lymphadenopathy in the lungs; enlargement of viscera, or bony lesions. The disease is almost always fatal, rapidly in children and more slowly in adults

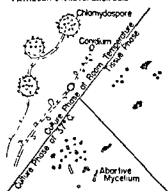
PATHOLOGY

It has not yet been possible to study adequately the pathology of the primary forms if such exist; this phase of the subject has been discussed as far as possible under the heading "Clinical Characteristics." The disseminated granulomatous form has been well delineated, however.

1 Gross pathology —The essential lesion is a granulomatous nodule which tends to ulcerate, a common site is in the intestinal mucosa, where the lymphoid patches seem to attract the fungus because of its preference for reticuloendothelial structures The lungs are almost always diseased and present miliary pseudotubercles, consolidations simulating tuberculosis, and hilar lymphadenopathy The bone marrow is uniformly diseased Extensive involvement of the adrenals may be encountered, where coalescence of several small foci often results in extensive necrosis Pseudotubercles may be seen in the liver, spleen, or kidneys In some cases the most impressive lesions are those of the mucous membranes or skin.

2 Histopathology —H. capsulatum is rarely seen extracellularly, it is an endoparasite of cells, preferably of the reticuloendothelial system, it is the only pathogenic fungus with this predilection. It appears as a round or oval body, varying from 1 to 3 microns in diameter, in which nuclei cannot be demonstrated, surrounded by a capsule which usually remains unstained. Singly budding forms may be seen Although staining with hematoxylin and eosin usually suffices, Gram's method or Giemsa or Bauer's stain (Lillie) will reveal the structure of the organisms more distinctly

or exudates. It is advisable to inoculate suspected material on a variety of media, including veal or beef infusion broth fortified with glucose and Sabouraud's glucose agar with and without added blood, streptomycin, and penicillin; duplicate specimens on all media should be maintained at 37 C. and at room temperature. Growth begins so slowly that cultures should not be discarded as negative until several weeks have elapsed. In broth tubes tiny clumps are formed, appearing somewhat cottony near the surface when at room temperature. The blood agar preparations held at incubator temperature first show small, yeastlike moist white colonies Microscopically these are seen to consist of small round or oval cells reproducing by



single buds. Some of these buds are much elongated and represent abortive attempts to produce the hyphae of the mycelial phase. With care and frequent transplantation, this yeastlike phase can be maintained at 37 C. indefinitely.

At cooler temperatures, the fungus grows only in its mycelial phase, slowly producing a white, cottony mat of aerial mycelium indistinguishable from many other fungi. Older colonies may assume a dirty brownish tint. Microscopic examination of these hyphae reveals them to be septate and to bear conidia of two kinds Small (3 microns) round or pyriform spores borne on short conidiophores or directly from the hypha are seen early Later, large (8 to 15 microns) rounded, thick-walled structures appear; these are covered with irregular, warty protuberances (vaguely resembling [illegible] l are called tuberculate [illegible] These are diagnostic of [illegible] ...epedonium is excluded

The yeastlike phase can be easily converted to the mycelial phase by removing the culture from the incubator to room temperature. The mycelial phase can sometimes be converted to the yeastlike form by fresh transplantation and subsequent incubation at 37 C; oftener it is necessary to

A study of sections stained by the Hotchkiss-McManus method led Pillsbury and Kligman to suggest that there is a "cell wall" peripheral to what has been considered to be a capsule; what has heretofore been thought to be the organism is thus really the nucleus, and the "capsule" is the cytoplasm. Occasional organisms are as large as 5 microns in diameter, especially in tissues from African cases, causing some speculation as to the existence of different species of Histoplasma The appearance of the organism does indeed suggest a relationship to Leishmania donovani and explains the early confusion. Leishmania, however, does not produce buds and has its distinctive linear blepharoplast. H. capsulatum may also be confused with Toxoplasma gondi; the crescentic forms and the absence of buds in the latter and the difference clinically in the diseases are of value in differentiation.

Around masses of parasitized cells, granulomas of the pseudotuberculoid type develop, consisting of caseous material surrounded by a zone of granulation tissue composed of lymphocytes, plasma cells, fibroblasts, macrophages, epithelioid cells, and giant cells Several such foci may coalesce to form large necrotic areas. There is sometimes evidence of healing by fibrosis, suggesting the possibility that in some mild cases the patient may recover without the disease being recognized.

MYCOLOGY

Like so many other fungi capable of causing deep mycoses, H. capsulatum is strictly biphasic in its life cycle. In the tissues it exists only in the yeastlike phase already described, exhibiting but one reproductive process, that of the production of single buds This phase is maintained almost uniformly in cultures which are held at body temperature (37 C.), although abortive attempts to initiate mycelial threads are commonly seen. At cooler temperatures, the growth is entirely different, consisting exclusively of hyphal threads forming a mycelial mat, reproduction in this phase is by means of specialized conidia

1 DIRECT MICROSCOPIC EXAMINATION —Direct examination of sputum or pus is rarely useful, it is almost impossible to identify the tiny, budding organisms with certainty in the midst of such debris, even after clearing the specimen with potassium hydroxide Smears of peripheral blood may, however, be advantageously examined if stained with Wright's or Giemsa's method Both thick and thin smears should be prepared, and the method of centrifugation to yield the "buffy coat" as employed in malaria may be helpful Material obtained from splenic puncture or from bone marrow may be similarly treated, as well as imprints and scrapings from tissue removed for biopsy from lymph nodes or mucocutaneous lesions. The large mononuclear cells are the most frequently parasitized.

2. CULTURAL CHARACTERISTICS —It is somewhat difficult to obtain cultural growth of H. capsulatum on primary isolation from animal tissues

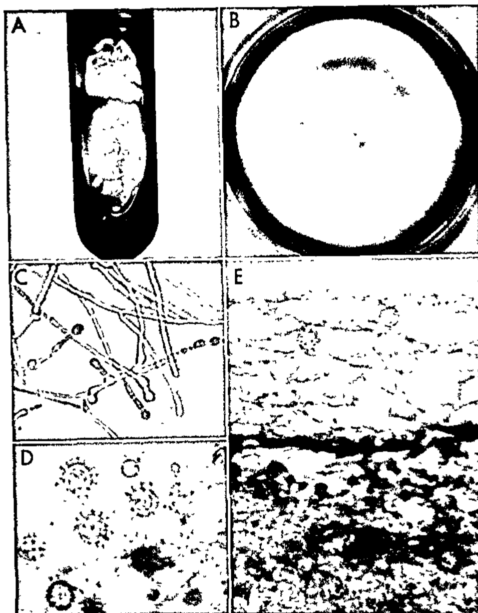


Fig 105 Histoplasma capsulatum **A**, growth in blood agar at 37 C After four weeks, colony is dull red and compact When agar is thin a white duvet develops **B**, fluffy, white colony on dextrose agar at five weeks **C**, culture mount showing vegetative elements, × 480 **D**, spiny chlamydospores in culture mount from cornmeal agar, × 1,000 **E**, section through colony with chlamydospores in fringe, × 500

infect an animal and implant directly from its tissues onto incubated media.

3. Animal inoculation.—Intraperitoneal injections of suspected material into young mice or guinea pigs may reveal the diagnosis when direct cultural methods fail. Lesions develop in the mesenteric lymph nodes and viscera, from which diagnostic smears, cultures, or histopathologic preparations may be obtained. Rats resist histoplasmosis completely, according to Königsbauer, and may subsequently serve as carriers.

IMMUNOLOGY

The present trend indicates that histoplasmosis probably is acquired by large numbers of persons, remaining very mild in all but a few, while conferring a lasting immunity. As in coccidioidomycosis, it seems likely that in those few persons in whom the fatal disseminated form develops it does so because of the possession of some inherent defect in immunologic mechanisms In coccidioidomycosis there is as yet no clue to the nature of this defect; but it has been repeatedly pointed out that disseminated histoplasmosis is frequently associated with other diseases of the reticuloendothelial system, such as leukemia, lymphosarcoma, or Hodgkin's disease. A logical explanation is that the lymphoblastomatous process causes the reticuloendothelial system to fail in the performance of one of its most important duties, the production of some specific antibody necessary for the development of immunity. Wilkerson saw statistical correlation of disseminated histoplasmosis with carcinoma both in man and in cattle. It is possible, although unlikely, that the reverse is true and that histoplasmosis may actually be the cause of some cases of lymphoblastoma. It has been noted that histoplasmosis is associated with other granulomatous disorders, especially tuberculosis, more often than coincidence would indicate, as is also the case with other deep mycoses.

At the present time, owing to lack of adequate material for pathologic studies, investigations in histoplasmosis are heavily dependent upon reactions to an antigenic substance, histoplasmin, which is extracted from cultures of *H* capsulatum in a manner identical with that employed in the manufacture of old tuberculin and coccidioidin. Unfortunately, there have been wide variations, both qualitative and quantitative, in the potency of the histoplasmin preparations heretofore available, and no rigid criteria for standardization have been adopted This fact must be kept in mind in evaluating all statistical studies, especially the earlier ones, since it is likely to explain many puzzling discrepancies, particularly with regard to whether or not the histoplasmin test is specific for histoplasmosis

During each of the past few years, more and more evidence has been accumulated to indicate that the serologic, allergic, and immunologic phenomena associated with histoplasmosis closely resemble those of coccidioidomycosis, a surprising fact in view of the differences in the pathologic

It is obvious that the subject of histoplasmosis is at present one of the most rapidly expanding frontiers of medicine. The next few years will undoubtedly bring further realization of its importance. It is to be hoped, also, that it has much to contribute to the better understanding of immunologic processes in general.

DIFFERENTIAL DIAGNOSIS

The primary pulmonary form must be differentiated when mild from the common cold, influenza, and bronchitis and when more severe from tuberculosis, bronchopneumonia, and other deep mycoses. It is possible for cultural procedures to reveal H. capsulatum in sputum, but better methods are needed than those available. If the intracutaneous histoplasmin test can be shown to yield no reaction at the onset of the disease and to elicit a positive reaction a short time later, the diagnosis of histoplasmosis seems warranted.

The disseminated form must be differentiated from neoplastic disease, leukemia, Hodgkin's disease, tuberculosis, syphilis, leishmaniasis, and the other deep mycoses The most accurate method of making the diagnosis is isolation of the fungus from infected material, which is not always easily accomplished. It should be attempted from blood, bone marrow, sputum, gastric content, and biopsy specimens, the techniques outlined in the discussion of the mycology of H. capsulatum being used (*see* p 325) Inoculation of guinea pigs or mice may be necessary. The organisms may be identified in histopathologic sections or in smears of blood, marrow, or material from splenic or liver puncture

A positive reaction in high titer to the complement fixation histoplasmin test is presumptive evidence of the presence of histoplasmosis, allowance must be made for possible nonspecific reaction

PROGNOSIS

The outlook in the primary pulmonary form is apparently excellent. The disseminated granulomatous type almost uniformly results in death.

THERAPY

The acute primary pulmonary form is too poorly recognized and understood to have afforded any guides for treatment In the vast majority of [illegible]

[illegible] mins, principally of the B complex series, will probably enhance resistance and the development of immunity Antibiotics of fungal origin should be withheld unless there is evidence of concomitant bacterial disease for which

propensities of the two diseases. The facts concerning these features are much more firmly established in coccidioidomycosis, largely because they began to be intensively studied some 12 years earlier; valuable clues derived thereby are accelerating progress in the study of histoplasmosis

Histoplasmin has been most extensively studied when employed as an intracutaneous test with 0.1 cc. of a 1:1,000 or 1:100 dilution. Immediate wheal reactions have been observed, but their significance is not known The delayed tuberculin type of response, consisting of the appearance of an erythematous papule at least 5 mm. in diameter in 48 hours, is considered positive. In many parts of the world, large groups of persons have been tested in this manner, including significant numbers from all age groups and of persons apparently free of all disease as well as others suspected of or known to be harboring histoplasmosis. The percentage of positive reactors encountered varies tremendously in different geographic locations, from practically zero to almost 80 per cent; furthermore, the incidence increases sharply at each step in the age groups from infancy to adult life. In the light of knowledge of tuberculin and coccidioidin reactions, these facts can be explained only by concluding that positive reactors to histoplasmin either are, or have been previously, infected with histoplasmosis. There must be some reservations until the specificity of the reaction is better established, but at least a portion of the nonspecific or "cross reactions" reported occur in persons harboring other diseases and may be avoided by better standardization of the antigen and use of the higher dilutions. Many persons reacting positively to histoplasmin present evidence of pulmonary calcification, previously unexplainable but now logically attributable to the benign form of histoplasmosis There have been some opportunities of testing persons early in the course of pulmonary infections with histoplasmosis, particularly those acquired in mycology laboratories The sensitivity apparently begins to develop within two weeks. Although not proved, it may be useful also to assume that a positive reaction to the histoplasmin test quantitatively parallels the specific immunity to reinfection, as is thought to be the case in coccidioidomycosis. Such reactivity apparently may last for many years.

The complement fixation reaction, especially standardized histoplasmin being used as the antigen, is being actively investigated. While its status is not yet well clarified and some reservations must be held with regard to specificity, it seems possible that the titer can be correlated with the severity and extent of the disease present at the time the test is performed, a situation also paralleling experience with coccidioidin

Thus the interplay between the degree of response to the intracutaneous test (indicating immunologic resistance) and the complement fixation test titer (indicating the extent and severity of the disease present) may prove of value in prognosis as it does in coccidioidomycosis.

Precipitin and agglutination reactions utilizing histoplasmin have not been sufficiently investigated to yield any conclusions

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they are specifically indicated; they may be harmful. Cortisone and corticotropin are contraindicated because of probable interference with resistance and development of immunity.

There is no specific therapy for disseminated, granulomatous histoplasmosis. Favorable results have been attributed to sulfonamides. More recently ethyl vanillate has been reported of benefit in a series of several cases. The disease is being so extensively studied that better therapeutic methods are almost certain to be forthcoming in the near future. A review of the most recent literature is therefore mandatory before treatment is outlined.

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that, instead, it is acquired in a mild form by almost all persons who are exposed to it, only about 0.1 per cent of whom ever become seriously ill in the previously observed manner. In recent years, C. E Smith and Kessel and their co-workers have clarified the allergic and immunologic aspects.

ETIOLOGY

Coccidioidomycosis is caused by a single species of fungus, Coccidioides immitis.

Stiles named the organism Coccidioides because its appearance in histopathologic sections resembled Coccidia, a group of protozoa pathogenic for animals and fowls, usually species of the genera Eimeria or Isospora. The similarity of these names still causes confusion, and the term "coccidiosis"

idioidosis"

preferred,

"immitis"

is literally translated as "not mild'; really, in accordance with Latin negatives, it means the exact opposite of mild, or "fierce "

DISTRIBUTION

The most important endemic area is the San Joaquin River Valley in south central California, others have been defined in Los Angeles County, Arizona, Nevada, New Mexico, Texas, and the northern states of Mexico. There is also an endemic region in the Gran Chaco region in South America. Persons of all ages seem equally likely to acquire the disease, but it is encountered in its more serious phases predominantly in males in the third and fourth decades, in the more deeply pigmented races, and in those whose occupations expose them to the inhalation of dust.

EPIDEMIOLOGY

C immitis has been cultured repeatedly from the dust of endemic areas, indicating that the soil is its natural habitat.

The factors which keep its occurrence in nature so closely confined to certain geographic localities are still not well understood but are nevertheless of great epidemiologic importance. The nutritional requirements of the organism are so simple that it grows luxuriantly on any soil from which its fungal and bacterial competitors have been excluded by previous heat sterilization It will also grow on a significant proportion of unsterilized soil specimens selected from many points on the globe Its failure to grow in the remainder is not demonstrably due to naturally produced antibiotics. The discovery that within an endemic area in Arizona certain rodents commonly harbored the infection led Emmons to suggest that these animals serve as endemic hosts and are the determining factors in the maintenance

32. Coccidioidomycosis

(San Joaquin Valley Fever, Coccidioidal Granuloma)

IN CERTAIN "endemic" localities dust borne on the wind during the dry season carries spores of the fungus Coccidioides immitis Inhalation of this material results in a disease capable of exhibiting almost as wide variation in its clinical manifestations as tuberculosis, which it resembles in many respects.

Although rarely encountered elsewhere, this disorder is worthy of study by all practitioners of medicine because certain of its allergic and immunologic characteristics are so constant, well defined, and subject to informative correlation with its clinical course that its investigation seems to offer valuable clues which may lead to a better understanding of the discouragingly complicated immunology of other more prevalent and important granulomatous diseases. There is ample time for a person who has inhaled the fungus spores to travel to any other spot on the globe before symptoms appear, the correct identification of such a case is not difficult and will often spare the patient unnecessary or harmful therapeutic measures and afford much reassurance as to prognosis. The ability to recognize the disease in a nonendemic locality will bring great credit to the diagnostician among his colleagues

HISTORY

The first case of coccidioidomycosis was reported from Argentina by Posadas and Wernicke in 1892 Rixford discovered a case in California in 1894 and together with Gilchrist published an extensive study in 1896 A few new instances were reported yearly during the next four decades, in most of which death resulted from widespread involvement.

The disease was considered to be a very rare, chronic, wasting, highly fatal granulomatous disease until 1935, when Gifford and Dickson showed

illness so slight as to remain unnoticed; a large percentage produce only mild symptoms and are considered by patient and physician to be "colds" or influenza. The remainder cause pulmonary symptoms and signs of any degree, none of which is specific for this disease. Malaise, fever, chills, nonproductive cough, night sweats, nasopharyngitis, pleurisy and other chest pain, headache, and backache are common symptoms.

A wide variety of pulmonary pathologic changes occur, including combinations of pleurisy, effusion, hilar thickening, parenchymal nodules, bronchopneumonia (or, at times, lobar consolidation), cavitation, and miliary scattering. Signs revealed by auscultation and percussion tend to be less pronounced than the actual changes present would indicate. Pleuritic rubs, suppression of breath sounds, râles, and dullness may be elicited

Although X-ray examination is frequently negative, even in well-developed cases, it may reveal a wide variety of combinations of abnormalities, most of which cannot be differentiated from those due to other pulmonary diseases. In mild cases, a fuzzy, peribronchial infiltration in the hilar region is the commonest finding. In severer cases, a soft, homogenous, bronchopneumonic infiltration is characteristic, somewhat favoring the middle and lower lobes in contrast to tuberculosis The pneumonic process rarely is lobar in distribution Isolated, well-circumscribed nodular lesions are frequently seen, concentrated in the middle and lower lobes, suggesting foci of metastatic malignancy or primary tuberculous lesions. Cavities, [illegible]

can be discovered in planograms Mediastinal and hilar adenopathy is not frequent but may be sufficient to make it difficult to distinguish the condition from Hodgkin's disease. Pleural effusion is seen in about 20 per cent of cases but is usually minimal and evanescent.

Other laboratory procedures are of little value in diagnosis or prognosis. Aside from the eosinophilia seen in association with the specific hypersensitivity to be mentioned on page 345, the blood count and sedimentation rate are as would be expected in any acute pulmonary illness not of virus origin

In from six to 16 days after the onset of symptoms, erythema nodosum (known colloquially as "the bumps" of "valley fever") or other typical form of erythema multiforme (morbilliform, urticarial, bullous) develops in up to 30 per cent of cases, oftener in light-skinned persons and in women. These eruptions are allergic and are caused by the hematogenous dissemination to the skin of a toxic substance derived from the fungi in the active pulmonary focus, acting in conjunction with hypersensitization. Living fungi probably are not carried to the skin in this process, at least they cannot be found in the lesions which result These are, therefore, "coccidioidids" in the manner of "dermatophytids" or "tuberculids" Acute arthritis occurs occasionally through the same mechanism. A significant degree of blood

and spread of the soil contamination. In California, however, infection among similar animals is apparently rare, and the same species of rodents are found in nonendemic areas. One prerequisite for an endemic area seems to be a climate having long enough periods without rainfall to keep vegetation sparse during certain seasons and allow dust to be borne on the wind in quantities. Until this subject is better understood, the possibility must be borne in mind that new endemic regions might become established in suitably arid districts by implantation of the organism into the soil, as by the burial of the unembalmed body of a person who had died of this disease, from sputum, or even by spores borne from laboratory cultures. It is possible that the "discovery" of the disease in 1892 was actually its first occurrence and that the endemic areas charted at intervals since that time actually represent spreading of the soil infection from the original focus.

From this exogenous soil source, the infection enters the body almost exclusively by the inhalation of spores carried in dust, causing what is called "primary pulmonary coccidioidomycosis." As would be expected there is a sharp increase in incidence in the late summer months, the so-called dusty season The "primary cutaneous" form, resulting from direct inoculation of the fungus into the skin, occurs rarely.

Measures effective in controlling dust where persons must work can markedly reduce the incidence of the disease. The installation of lawns or other vegetation, the paving of dusty surfaces, the use of hygroscopic substances, and simply "wetting down" the dust are helpful. Masks may be worn where the risk is great

Transmission from living man to man has not been observed, although it is certainly possible, a mortician is known to have acquired a primary cutaneous infection from a cadaver. Wild rodents, cattle, dogs, and sheep are frequently infected, but no authentic instances are known of the transmission of the disease to human beings from such sources.

CLINICAL CHARACTERISTICS

Coccidioidomycosis resembles tuberculosis in many of its clinical manifestations, the principal differences lie in its avoidance of the intestinal tract and its failure to exhibit sarcoidal forms It is necessary to differentiate sharply between the "primary" stage, which occurs frequently, and the "disseminated" or "granulomatous" type, which occasionally follows.

1 PRIMARY PULMONARY COCCIDIOIDOMYCOSIS —Almost all previously uninfected persons who inhale the fungus in a significant quantity acquire the disease. The incubation period is from 10 to 14 days Among persons born in or moving into endemic regions, the "skin test" (which will be discussed in detail on p 345) reveals an increase in the percentage of positive reactors for each year of their residence, the percentage often reaches 90 within three or four years More than half of the infections result in an



... Coccidioidomycosis (C. immitis), primary cutaneous (chancriform) inoculation. A, ... discrete pap-

... maining photographs by Avis Gregerson, ...

eosinophilia is commonly found in connection with this reaction. Patients who exhibit any of these phenomena are virtually certain to recover from the disease completely and rapidly; the significance of this most important fact will be discussed further under the heading "Immunology" (*see* p. 345).

Almost all patients who acquire primary pulmonary coccidioidomycosis recover completely, without sequelae except that they are apparently immune to reinfection for many years, probably for life. In a small percentage, approximately one per thousand, the disease progresses into the disseminated, granulomatous form to be discussed presently.

Recovery may be delayed for some months in patients exhibiting extensive pneumonic infiltration, parenchymatous nodules, or large cavities. Such patients must be carefully guarded against resuming activity prematurely, lest they lose the chance of recovery. They should also be watched closely for evidence of dissemination.

2. Primary cutaneous coccidioidomycosis.—Although it was long believed that infection was frequently caused by direct inoculation of Coccidioides into the skin, such infection is probably extremely rare. It is true that a lesion in the skin is often the first manifestation of the disease, but the subsequent course of events in almost all reported cases strongly indicates that the fungus was brought to that point by being disseminated from a previously unrecognized primary pulmonary focus, a type which, it will be recalled, frequently remains subclinical

Wilson, Smith, and Plunkett observed a most instructive case, that of an embalmer who acquired the infection in an abrasion on his finger while embalming the body of a person whose organs were extensively involved. An indurated, almost painless chancre similar to that due to syphilis or sporotrichosis developed at the inoculated site, accompanied by a mild fever. Shortly thereafter, eight nodules appeared along the lymph channels draining this area, followed by epitrochlear and axillary lymphadenopathy simulating sporotrichosis The organisms were recovered from several sites The entire syndrome subsided spontaneously, in a manner conforming to that usually observed when the primary lesion is in the lung. Indeed, it seems probable that when the skin is the portal of entry, the infection should be benign in as large a percentage of cases as it is in the primary pulmonary form In contrast, it is considered significant that most of the cases previously thought to have originated in the skin "progressed" to the disseminated form, which indeed they probably were when first observed One exception seems to be the case reported in 1927 by Guy and Jacob, which resulted from a puncture wound into the thumb by a cactus thorn Recently, Trimble and Doucette observed the same chancriform syndrome resulting from an intracutaneous inoculation in a laboratory worker

3 Disseminated coccidioidomycosis, coccidioidal granuloma — For reasons most of which are not clear, an occasional patient with primary pulmonary coccidioidomycosis fails to fight the disease immunologically.



... variety. A, Large subcutaneous ... of nose ... age, ... ions

sustains more and more pulmonary involvement, and finally acquires other lesions by hematogenous dissemination of the living organisms to the skin, bones, central nervous system, or viscera. In striking contrast to the previously described benign primary form, this type is fatal in perhaps 50 per cent of instances.

Although the inhalation originally of massive amounts of fungus spores cannot be excluded as a significant factor, the principal cause of dissemination seems to be the possession by certain persons of an immunity mechanism which is inherently defective in some vital feature. Whether or not dissemination is to occur is apparently determined early in the course of the infection, probably by an immunologic deficiency present even before it was acquired. Failure to recognize the primary infection and to guard the patient against premature overactivity may also play a part Males are much more likely to sustain dissemination and to succumb, and the incidence increases in proportion to the depth of pigmentation in the skin Filipinos, however, resist the disease less well than much darker-skinned Negroes. (It is worth recalling that the allergic "coccidioidids," considered to be so indicative of a good prognosis, are encountered less frequently in men and in the more deeply pigmented races.)

Dissemination may occur early in the course of the disease and be rapid and massive, resulting in a multitude of small foci widely distributed throughout the body, simulating miliary tuberculosis, and leading to early death. All degrees of dissemination in rate and extent are encountered between this picture and the other extreme, represented by a solitary disseminated lesion developing long after the primary infection and progressing slowly or even intermittently Many such lesions eventually heal, and some patients recover completely; in others more foci develop, enlarge, and ultimately cause death, sometimes within a few months, sometimes only after several years

The organs most likely to be involved by dissemination are, in the order named, the lungs, skin and subcutaneous tissues, bones, joints, viscera, meninges, and brain The discovery of extrapulmonary lesions indicates dissemination except in those extremely rare instances in which the skin furnished the portal of entry. In contrast to the situation in tuberculosis, the gastrointestinal tract is remarkably resistant to coccidioidal infection both through the ingestion of spores of the fungus and by hematogenous dissemination

In the lungs, dissemination is to be suspected when pneumonic consolidations progress rapidly, when mediastinal adenopathy is marked and progressive, and when infiltrations resembling the adult type of pulmonary tuberculosis develop, particularly in the apices. Lesions in bone are prone to select points of tension or pressure, such as the insertion of ligaments or tendons, they are characteristically "punched out" and cystic in appearance, with a sharp peripheral line of transition from normal bone to complete destruction, in contrast to the "fuzzy" edges of some other destructive

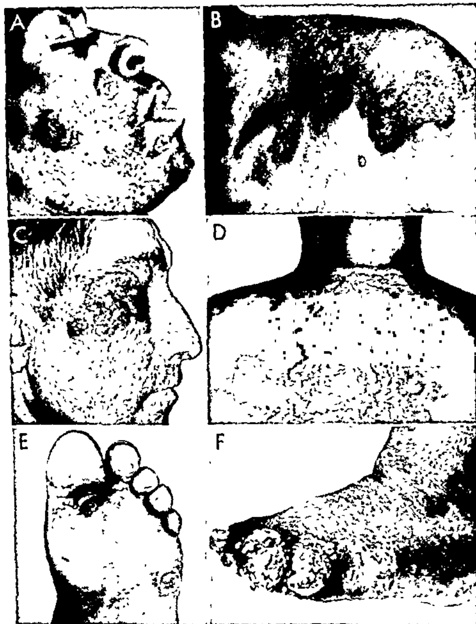


Fig. 108 Coccidioidomycosis, chronic granulomatous lesions A and B, well-defined plaques in Mexican patient C and D, lesions in this patient tended to coalesce and form large areas of involvement E and F, discrete and fungating lesions on feet. (*Courtesy of Drs C F Lehmann and J L Pipkin*)

processes. Sometimes these lesions extend to involve joint cavities, resembling then tuberculous arthritis, and in this instance, selecting the non-weight-bearing areas. In the skin, dissemination produces subcutaneous abscesses which develop slowly and after incision or spontaneous rupture leave chronic, indolent, draining sinuses Around these lesions the skin frequently becomes additionally infected, the picture simulating scrofuloderma Frequently the skin becomes involved by dissemination without a preceding subcutaneous abscess By slow extension, large areas may ultimately be involved in an ulcerative, granulomatous process exhibiting irregular serpiginous borders and central dense scarrings The sudden appearance of verrucous, granulomatous lesions on the face or trunk was observed by Epstein to indicate death within a few weeks or months due to voluminous miliary spreading.

Lesions in the viscera usually occur as part of a widespread dissemination, and the clinical signs seldom point to one organ. Meningitis is the commonest form involving the central nervous system and is almost always fatal, although occasionally slow in its progress. Light-skinned persons sustain *dissemination less frequently, but when they do, meningitis is the* predominant form In all types, fever, chills, prostration, anorexia, and progressive emaciation are typical symptoms

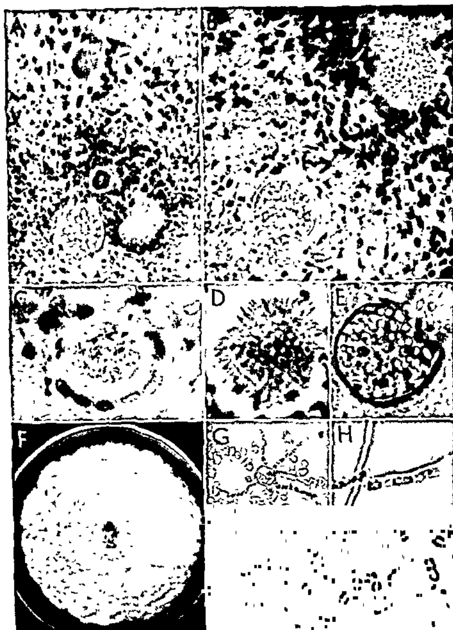
A hypochromic anemia is commonly encountered. The leukocyte count is variable The sedimentation rate is usually maintained at a high level during the course of the disease

PATHOLOGY

Because of the excellent prognosis, it has not been possible to study extensively the pathology of primary pulmonary coccidioidomycosis in its milder forms except by interpretation of roentgenographic findings When the allergic "id" reaction occurs, the lesions available for examination, usually those in the skin, are characterized by a polymorphic infiltrate containing many eosinophils but lacking the causative organisms

In the progressive disseminated form, the gross pathologic changes *range from abscess formation through granulomatous infiltration* to healing by fibrosis, all stages and all sizes of such lesions are commonly encountered simultaneously The distribution of these foci has been discussed in the section on clinical characteristics.

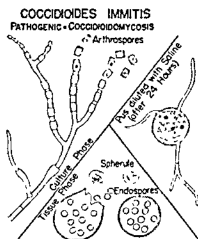
Histopathologic study of lesions reveals the organisms in variable numbers surrounded by a cellular reaction usually classed as of the "mixed" type, varying from an acute, purulent reaction in some foci, in which poly- [illegible] [illegible] ture in nearby lesions It will be seen that these alterations in the type of infiltrate follow closely the life cycle of the parasite (*see* p 344) Immediately after a spherule ruptures and discharges its endospores, numerous



dextrose agar after one month G, endospore germinating in culture H, I, and J, culture mounts revealing characteristic short segments

polymorphs invade the area and an acute suppurative reaction results. As these endospores enlarge and become mature spherules, the reaction around each one becomes ever more chronic, until it is finally tuberculoid and granulomatous just before rupture occurs. The organisms may be seen in huge numbers in material from persons succumbing rapidly to the disease; conversely, they may be very sparsely distributed and difficult to discover if the disease is progressing but slowly against much immunologic resistance.

Cutaneous lesions show considerable pseudoepitheliomatous hyperplasia, this is usually not as pronounced, however, as in North American blastomycosis.



MYCOLOGY

Coccidioidomycosis is caused by a single species of fungus, Coccidioides immitis. Although some strains have been observed to be consistently less pathogenic for laboratory animals than others, there has been no correlation with the severity of the disease in the human hosts from which they were recovered

Direct microscopic examination may reveal the organisms rather easily in pus from subcutaneous abscesses or other cutaneous lesions It is much more difficult to find them in sputum, gastric contents, pleural exudate, or cerebrospinal fluid.

It is advantageous to prepare slides in two ways. For the first, a drop of exudate is mixed on the slide with a drop of 10 per cent potassium hydroxide, a coverglass placed over the mixture, and this area gently heated from below, a procedure resulting in "clearing" in the usual manner. Under subdued light the organisms appear as spherical bodies varying from 10 to as much as 80 microns in diameter, with a thick, highly refractive wall

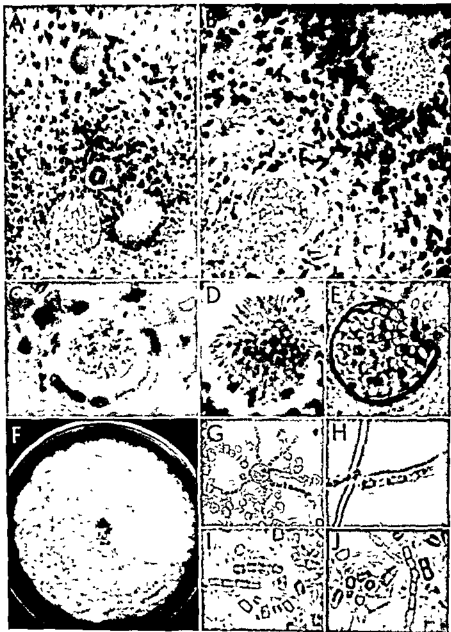


Fig 109 Coccidioides immitis A, section of spleen showing fungus in various stages

which becomes thinner in the larger specimens and sometimes is ruptured Small, nonsporulating spherules cannot be distinguished from the non-budding form of Blastomyces. The larger spherules are seen to contain many small (2 to 5 microns in diameter) globular "endospores," frequently presenting polygonal outlines due to pressure from neighboring cells.

When the parasites are sparse or the examiner is not intimately familiar with their appearance, it may be difficult to differentiate them from globular artefacts (e g., oil droplets) or other cells. In this event, a drop of exudate should be diluted with a drop of normal saline and placed beneath a coverslip the underedges of which have been coated with petrolatum by being drawn across the thenar eminence of the palm previously coated with this substance. Such a specimen will not dry out for several days at room temperature, and within 24 hours viable Coccidioides spherules will begin to "sprout," each sending out several threadlike hyphae. (Compare with B. dermatitidis, p. 298, each spherule of which produces a single thread) This method frequently yields a reliable diagnosis long before histopathologic preparations or cultures can do so.

In the tissues of living animals the fungus reproduces only by the formation of "endospores" within spherules (sporangia) which enlarge until the walls become so thinned as to rupture. Each endospore enlarges in turn (often even before it is discharged from the mother cell) and becomes a mature sporangium This entire cycle of the pathogenic phase is easily studied in histopathologic sections from the viscera of persons who have died rapidly of the disease, the organisms are present in large numbers in all stages of development. The spherule wall does not stain well with hematoxylin, but the endospores do The Hotchkiss-McManus stain shows the organisms beautifully.

1 CULTURAL CHARACTERISTICS —Suspected material should be inoculated into Sabouraud's glucose agar and allowed to remain at room temperature The fungus grows slowly but is usually successful in overcoming its competitors. If but few organisms are present in highly contaminated material, the special medium advocated by Ajello and Georg is advantageous At first the colonies are thin, translucent, and moist, resembling wet tissue paper, but shortly a fuzzy dry aerial mycelium develops, white in the earlier stages but soon becoming a dirty brown or gray It never looks well groomed but always appears "moth-eaten." In contrast to Blastomyces, Histoplasma, and Sporotrichum, there is no variation in the appearance of cultures because of differences in the temperature at which they are grown

In from three to 14 days most strains sporulate, and on microscopic examination short, specialized hyphae, thicker than the usual threads, can be seen, each bearing terminally a few "arthrospores" (jointed spores) suggesting a string of beads These arthrospores are somewhat barrel-shaped and are separated from each other by a narrowed collarette distinctive for this fungus (*cf* Geotrichum, p 430) It is well to insist on finding evidence of fragility by observing such spores to have broken away from each other,

since the hyphae of many fungi are divided into short segments by cross walls which may be confused with arthrospore formation. These arthrospores are usually the only means of reproduction of the fungus in its saprophytic phase. Great care must be exercised in handling dry fluffy cultures, since they contain many arthrospores, they are easily borne on the air and are highly infectious if inhaled by nonimmune persons. It is in this form that they are carried with dust on the wind and cause the usual primary pulmonary infection by inhalation.

2 ANIMAL INOCULATION —Intraperitoneal injection of infectious material into mice results in a widespread disease which is diagnostic, occasionally even when other measures fail, and the inoculation of portions of cultures will confirm the pathogenicity of the organism when it is in doubt Tissues from such animals usually contain myriads of the easily identified spherules

IMMUNOLOGY

Even when the primary pulmonary infection is so mild as to be without clinical manifestations, it apparently confers a complete immunity lasting for many years in all but one or two per thousand cases Beginning after a week or two and accompanying this process is the development of hypersensitivity to the intracutaneous injection of an extract of cultures of C immitis called "coccidioidin," prepared in the same manner as "old tuberculin" A rough quantitation of this reactivity is obtained by using 0 1 cc. of various dilutions (1 1,000, 1 100, 1 10) a few days apart, beginning with the weakest to prevent unduly severe reactions, especially when erythema nodosum or multiforme is present Clinicians have long utilized the degree of this hypersensitivity as a measure of the patient's immunologic resistance to the disease, although there is insufficient evidence to conclude that the one depends on or always parallels the other The reactivity is retained for many years, perhaps for life

Coccidioidin especially standardized for the purpose can be utilized as the antigen in a quantitative complement fixation reaction like the Kolmer modification of the Wassermann test Positive reactions are not obtained for the first two or three months of the disease, after that the quantitative "titer" thus determined serves the clinician as a measure of the severity of the infection and the extent to which it has spread Cure cannot be considered certain until it has subsided to negativity

Using the interplay between the reaction to the skin and complement fixation tests repeated at intervals of about a month, one can make a much more accurate prognosis than by relying on any other combination of clinical observations, X-ray pictures, or other laboratory procedures A highly positive skin test and negative complement fixation reaction indicate an excellent prognosis in spite of severe clinical illness, a negative reaction to the skin test and a high-titer response to the complement fixation test mean

probable death by dissemination, even when the patient appears entirely well by clinical examination.

Positive reaction to a precipitin test using coccidioidin as the antigen can be obtained within a week or two and constitutes one of the earliest means of diagnosis. This reactivity disappears in a few months, however, without regard to the outcome of the disease, so that it has no prognostic value.

Coccidioidomycosis is unique in presenting useful reactions to such a battery of immunologic testing procedures. It is to be hoped that intensive study of its immunology will yield valuable clues leading to better understanding of some vastly more complicated granulomatous diseases of greater importance to mankind, particularly tuberculosis.

DIFFERENTIAL DIAGNOSIS

Coccidioidomycosis should be suspected whenever a person who has previously lived in or visited one of the endemic areas is found to be suffering from an obscure illness.

The primary pulmonary form must be differentiated from influenza, bronchitis, and the common cold and when severe from almost every other disease of the lungs. The disseminated type may resemble tuberculosis, syphilis, neoplastic diseases, and the other deep mycoses.

The diagnosis is assured when the organism is identified in exudates or tissue sections or recovered in culture. A positive reaction to the complement fixation or precipitin test or both is pathognomonic of active infection. Since the intracutaneous reaction remains positive for many years after complete recovery of the patient, it cannot be said to indicate active disease, however, the diagnosis can be made by observing its change from negative to positive during the course of an acute pulmonary illness.

PROGNOSIS

The outlook is excellent in the primary forms, although caution is necessary in the case of dark-skinned persons, especially males. The disseminated type carries a mortality rate of approximately 50 per cent Serologic studies and the skin test are excellent guides and may be relied upon more than clinical impressions

TREATMENT

The acute, primary pulmonary infection remains subclinical in most cases and requires no treatment, in the remainder all gradations of severity of pulmonary disease are encountered, for which appropriate, supportive, nonspecific medical and surgical measures should be selected on clinical grounds To enhance the development of immunity, emphasis is placed on

bed rest and adequate nutrition, including supplemental vitamin B complex, during the febrile period. Antibiotics of fungal origin should be avoided (unless specifically indicated by bacterial complications) until better knowledge frees them from implications of harmfulness. Antihistaminics may be utilized to relieve the symptoms of erythema nodosum or multiforme. Cortisone and corticotropin are contraindicated because of probable interference with resistance and immunity development.

1. COCCIDIOIDAL GRANULOMA.—In disseminated, granulomatous coccidioidomycosis the management is the same as that for tuberculosis of similar degree, the specific drug and antibiotic therapy being omitted and steroid compounds being avoided. Absolute bed rest, a high caloric diet

involved tissue has frequently been employed when the disease has appeared to be sufficiently localized, as in a single lung or lobe or in an extremity It cannot be denied that recovery has ensued in many instances, but it is also apparent when the prognostic significance of the interplay between the intracutaneous and complement fixation tests as recorded is analyzed that many of the patients would have recovered without surgery No method of therapy can be accurately evaluated without the ability to make a prognosis to be expected if it is withheld

2 VACCINES AND OTHER AGENTS —The use of coccidioidin as commercially available has not proved advantageous and may be harmful. Specially prepared vaccines, unobtainable generally, were said to be valuable by Jacobson and Stewart. Several drugs and new antibiotics are under study, none has yet been convincingly shown to be of specific value A careful evaluation of all recent publications should precede use of any such experimental drug.

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33. Cryptococcosis

(Torulosis; Busse-Buschke's Disease; European Blastomycosis)

A YEASTLIKE fungus, *Cryptococcus neoformans*, apparently widely distributed in nature, occasionally causes a human infection called cryptococcosis or torulosis, a chronic, wasting, highly fatal disease characterized by a pronounced predilection for involvement of the central nervous system It is probably of more frequent occurrence than the literature indicates, many cases being unrecognized because of lack of familiarity with its clinical manifestations and the details of its mycologic diagnosis

HISTORY

In 1894 and 1895 Busse reported an unusual case of a woman infected with a yeastlike organism, Buschke added further details in 1895 Although somewhat atypical by virtue of there being no central nervous system involvement, the case is credited as being the first observed instance of cryptococcosis, the organism was maintained in living culture, and in 1934 Benham showed it to be identical with other pathogenic strains of *C neoformans* Cases which were probably examples of torulosis were reported by Curtis in 1896, Von Hauseman in 1905, Furk in 1907, and Brewer and Wood 1908, but the first case which was accompanied by conclusive proof was that reported by Versé in 1914 Stoddard and Cutler in 1916 clearly delineated the pathology and clinical picture of cryptococcosis and differentiated it from the other deep mycoses Freeman contributed a valuable monograph in 1931, as did Cox and Tolhurst in 1946

ETIOLOGY

Although there is considerable variation among strains of the organism, it is usually conceded that cryptococcosis is caused by a single species of

fungus, Cryptococcus neoformans, named by Vuillemin in 1901. The generic name Torula, suggested by Weis in 1902, and the species designation histolytica, advocated by Stoddard and Cutler in 1916, have been widely used, although both terms are subject to considerable criticism.

DISTRIBUTION

Cryptococcosis has been reported from all continents and does not appear to be limited by geographic factors; in this regard it resembles actinomycosis and differs from the other deep mycoses. This fact tends to confirm the view that the infection is often endogenously acquired and/or that the organisms are widely dispersed in nature. It also suggests that the factors which determine whether or not infection takes place are peculiar to the individual host rather than to the fungus.

Cryptococcosis occurs in all decades of life, but predominantly between the ages of 40 and 60 years. Males are affected about twice as frequently as females. There is no apparent variation in susceptibility because of race or occupation

EPIDEMIOLOGY

Benham found that a number of strains of Cryptococcus isolated from various sources in nature differed morphologically, culturally, and serologically from several recovered from normal human skin, but that some of the latter could not be distinguished from specimens derived from fatal cases of cryptococcosis Emmons isolated from soil four strains of C. neoformans which were pathogenic for laboratory animals Fermenting fruit juices have yielded similar pathogenic strains (Sanfelice), and they have been isolated from milk by Klein and by Carter and Young Human infection has not been traced conclusively to any of these sources, but it appears likely that strains of C neoformans capable of pathogenicity are frequently present on the skin and mucous membranes of normal persons, awaiting the fortuitous combination of circumstances which allows infection to occur The factors of trauma and symbiotic alliance with bacteria which are so important in the predominantly endogenous deep fungous infection, actinomycosis, are not apparently operative in cryptococcosis There is, however, a resemblance to histoplasmosis, for cryptococcosis is associated more frequently than can be explained by coincidence with lymphoblastomas, principally Hodgkin's disease and the leukemias

Although animals acquire cryptococcosis by natural means, there has been no reported instance of human infection derived from animals Direct transmission from man to man has not been proved, although Cox and Tolhurst considered it not unlikely after discovering the organisms in the sputum in four cases

The route by which the fungus enters the body is obscure. Freeman,

reviewing the literature in 1931, stated the belief that the usual portal of entry is the lungs. In 1946 this view received strong support from Cox and Tolhurst, who demonstrated that the fungus could resist drying for at least 10 months and hence could be inhaled with dust. A history of a preceding respiratory infection can be obtained with statistically significant frequency from patients suffering from any form of cryptococcosis.

Direct inoculation through the skin or mucous membrane has been accepted as the method of entry by many authors when reporting cases, but in most instances features are cited which cast doubt on the validity of their assumption. The portal of entry has occasionally been shown to be the oropharyngeal or gastrointestinal tract.

C. neoformans has been cultured from the blood of infected persons, a fact indicating that the disease may be hematogenously disseminated Lymphatic spread occurs in laboratory animals but has not been proved in human beings Semerak suggested that meningitis might occur by direct spread of the organisms from the nasopharynx.

CLINICAL CHARACTERISTICS

Although cryptococcosis is best known because of its predilection for concentrating in the central nervous system, such involvement is often absent. The lungs are almost as frequently affected, perhaps even more so, and, since they probably afford the portal of entry in most instances, it is fitting that the pulmonary form of the disease be discussed first Involvement of bones, skin, mucous membranes, and viscera will be discussed in later paragraphs

1. PULMONARY CRYPTOCOCCOSIS —The clinical picture of pulmonary cryptococcosis cannot be differentiated from that of other chronic lung infections, except perhaps by its tendency to produce fewer symptoms than the extent of pathology demonstrated by physical signs or by radiography would indicate. There have been no observations which would suggest that a "primary" form could be differentiated from a "disseminated" type in the absence of proved extrapulmonary lesions A mild degree of fever is exhibited frequently, though by no means consistently, cough is sometimes present, and sputum is rather infrequently produced There is occasionally pleural pain and, rarely, effusion Physical signs usually indicate bronchitis or pulmonary consolidation, dullness and diminished breath sounds are commonly elicited, but râles or rhonchi are rare, since exudation is not common

X rays may reveal a wide range of pathology, from that consistent with minimal bronchitis to large, dense shadows with well or poorly defined borders suggesting neoplasm or abscess The linear markings may be accentuated and surrounded by snowflake-like woolly shadows. Small nodular shadows suggesting miliary tuberculosis or Boeck's sarcoid may be seen, as in other pulmonary mycoses, and, in contrast to tuberculosis, the favored

sites are the bases and mid-portions of the lungs, although the apices are sometimes affected. A majority of cases show bilateral involvement. Cavitation is rare. The mediastinum is not usually affected, in contrast to actinomycosis, blastomycosis, and coccidioidomycosis

In some cases the pulmonary involvement increases sufficiently to cause death, more frequently the infection becomes disseminated to the central nervous system or other organs. Some cases of pulmonary cryptococcosis have ended with recovery, leading Stoddard and Cutler, Sheppe, and other authors to conclude that there is considerable tendency toward healing in the pulmonary form. Since cryptococcosis is seldom suspected as the diagnosis of lung disease in the absence of extrapulmonary lesions, it is entirely possible that it actually occurs frequently and heals without recognition, as is known to be the case with some other deep mycoses. (*See* Chapters 31 and 32, on histoplasmosis and coccidioidomycosis.)

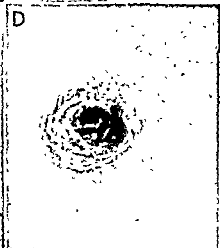
2. Central nervous system cryptococcosis —The signs and symptoms indicating invasion of the central nervous system are referable either to meningitis or to increased intracranial pressure. The earliest symptom is usually headache, intermittent and frontal at first, gradually becoming more severe, persistent, and generalized Sometimes the onset is sudden and violent, accompanied by projectile vomiting, at times suggesting subarachnoid hemorrhage. Vertigo, dizziness, and neck rigidity soon appear. Amblyopia occurs often and nystagmus, diplopia, and ptosis occasionally. Severe mental aberrations, such as restlessness, irritability, disorientation, and hallucinations, alternating with periods of depression and loss of affect, are common, sometimes a definite psychosis may be closely simulated, especially if appearance of the characteristic headache is delayed. Epilepsy has occasionally been observed

Focal lesions of the brain and occasionally of the spinal cord occur and may lead to a diagnosis of tumor if the more generalized symptoms are absent or mild, cryptococcosis has been diagnosed occasionally from material obtained during an operation for the removal of a "tumor" Such focal lesions may occur anywhere in the central nervous system, and the resulting signs and symptoms are accordingly so variable as to preclude discussion here, since they conform to ordinary neurologic topographical diagnosis Ataxia and hemiplegia are the commonest presenting features

Cryptococcic meningitis or meningoencephalitis may or may not be accompanied by fever, usually mild and irregular The pulse rate is less likely to be elevated by fever than depressed by the increased intracranial pressure The other usual signs of increased intracranial pressure are common Examination of the cerebrospinal fluid frequently proves the diagnosis The pressure is increased, the fluid usually yellowish or otherwise discolored, the cell count raised and predominantly lymphocytic, the protein increased, and the chlorides and sugar significantly diminished The colloidal gold curve may be normal or of the meningitic type. The


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characteristic singly budding cells of *C. neoformans* can often be seen by direct microscopic examination of centrifuged specimens, especially if these are mixed with India ink to contrast the capsule, or of the fungus recovered in culture. Without this careful laboratory confirmation of the causative organism, the entire picture is consistent with tuberculous meningitis, and this diagnosis has undoubtedly been erroneously made on many occasions.

Although there may be short remissions, the disease progresses slowly to death, usually in three or four months but sometimes only after one or more years. Recovery has not occurred in any case in which the diagnosis was established. However, it is entirely possible, and even considered likely by some authors, that many cases of mild infection may occur and recovery ensue without the disease being recognized.

3. CRYPTOCOCCOSIS IN OTHER ORGANS.—In about one-fifth of the cases there is associated enlargement of the lymph nodes, spleen, or liver. Frequently this is apparently unrelated to the infection and presents the picture of Hodgkin's disease or another lymphoblastomatous disorder. First noted by Fitchett and Weidman, this phenomenon has since been emphasized by many authors, until there is no longer any doubt that it occurs oftener (in approximately 10 per cent of cases) than can be accounted for by coincidence. The correct interpretation of this relationship is not clear It may be that cryptococcosis actually causes Hodgkin's disease or an indistinguishable syndrome in some cases, it has even been postulated that the capsular material of the fungus may contain substances whose liberation can induce malignant transformation It is more likely, however, that such a lymphoblastomatous process involving the reticuloendothelial system causes it to fail in the performance of some of its vital duties in the development of immunity and resistance, thereby allowing the infection to become overwhelming

Infection of the skin is uncommon in cryptococcosis, occurring in perhaps less than 5 per cent of cases. In some instances the skin has been accepted as the portal of entry, although conclusive proof has not been presented Most frequently reported has been an acneform eruption of the face, consisting of papules exhibiting a translucency suggesting vesiculation or appearing like basal cell carcinoma except that the border is sloping instead of abrupt There is finally necrotic destruction of the apices of these lesions, resulting in small ulcers which discharge a tenacious, translucent, grayish or brownish-red material, differing markedly from ordinary pus and consisting almost entirely of the encapsulated fungi with little or no cellular contributions from the host. Such ulcers may be surrounded with an elevated border of some width which has the translucent "pearly" appearance so frequently seen in basal cell carcinoma, with which such lesions have been clinically confused Similar lesions involving the mucous membranes have been described. Scaly eruptions resembling eczema or psoriasis have been reported in connection with cryptococcosis, but the

relationship has not been proved in any instance. A unique case reported by Wilk exhibited large, firmly indurated dark-colored plaques on the skin of the legs, which showed the fungi in large numbers on histopathologic examination. Cutaneous lesions have healed eventually in several reported instances and must not be considered as of such serious prognostic importance as central nervous system disease.

Cryptococcic involvement of bone was reported by Collins in 17 of some 200 cases The lesions were multiple and widely disseminated, producing osteolytic rarefactions, especially in bony prominences. Roentgenographically the appearance suggested sarcoidosis or coccidioidomycosis rather than the proliferative changes seen in actinomycosis or tuberculosis. There is little bony reaction. Occasionally material removed from such a "cystic" lesion has led to the diagnosis of myxosarcoma because of its translucent, glairy, sticky character, consisting as it does almost entirely of the encapsulated fungi Bony lesions have occasionally been observed to heal spontaneously.

Lesions have been reported in the kidneys, adrenals, pancreas, testes, bone marrow, and large blood vessels, and it is considered likely that such involvement occurs more frequently than it is observed, owing to the absence of symptoms or signs leading the pathologist to search diligently throughout all such areas of the body.

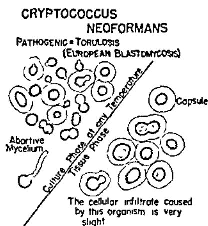
PATHOLOGY

In general, the most characteristic feature of the lesions of cryptococcosis is the mildness of the inflammatory response induced, indeed, inflammation may be almost absent, especially in brain lesions The body seems not to provide any cellular resistance to the invasion of the fungi, allowing them to proliferate freely until large localized masses are formed consisting almost entirely of encapsulated budding cells, with a few phagocytic cells and a coarse reticulum of lightly formed connective tissue trabeculae The cystic lesion is surrounded by a thin zone of granulomatous, lymphocytic reaction By such simple enlargement, these gelatinous "tumors" exert enough pressure on the surrounding tissues to make room for themselves, a process which was earlier thought to be histolytic in nature and due to a lytic toxin produced by the fungi, a theory which led Stoddard and Cutler to name the organism (Torula) histolytica Freeman and most later authors supported the simple pressure theory

1 Gross pathology —In the lungs, the gelatinous cystic masses described are frequently only one or two in number and up to 7 cm in diameter, occasionally they are multiple and small In addition, some cases show a fibrotic and granulomatous tissue reaction around small aggregates of organisms, lymphocytes, giant cells, and epithelioid cells are characteristic, but caseation is absent, in contrast to the picture in free tubercles It is evident that in these cases some degree of healing is occurring

In the central nervous system, the subarachnoid space is frequently distended by gelatinous material which renders the brain itself slippery to touch. In about half of the cases, the meninges are involved while the brain itself escapes Small granulomatous masses resembling tubercles may be found, or small cysts may project from the surface of the cortex. Gelatinous cysts occur in the previously described manner, usually small and multiple and seldom involving the white matter. The spinal meninges are involved frequently but the cord itself rarely.

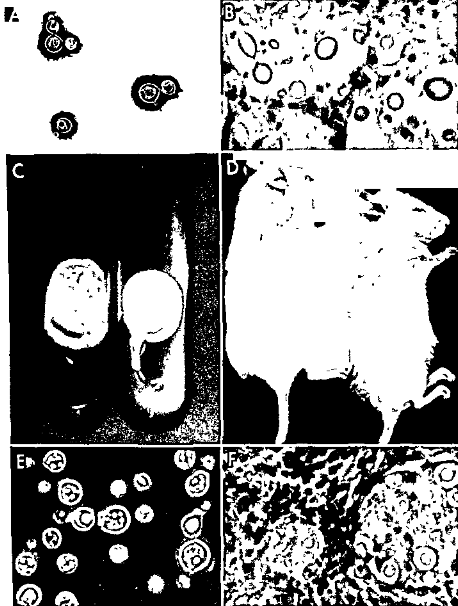
In disseminated cryptococcosis, small embolic lesions of either the granulomatous-fibrotic type or the cystic form without cellular reaction may be seen in the kidneys, adrenals, liver, pancreas, thyroid, testes, skin,



and aorta. In the spleen and lymph glands the lesions may be similar, but in addition many cases reveal the typical picture of Hodgkin's disease.

2 HISTOPATHOLOGY —C neoformans is usually easily identified in tissue sections because of the large capsules which surround the organisms. While the capsules themselves do not survive the usual fixation, sectioning, and staining procedures, becoming shrunken into a few strands radiating from thin layers around the organisms, the spaces in the tissues which they previously occupied remain The fungi are seen in the centers of such spaces and are oval to spherical, thick-walled structures, staining fairly deeply with the basophilic stain A small proportion will be seen to have been cut in the appropriate plane for one to observe the production of the characteristic single thin-walled budlike daughter cell

The cellular reaction is usually surprisingly slight and frequently almost absent Some cases, however, show a heavy, chronic inflammatory infiltrate, in some areas granulomatous and tuberculoid The gelatinous cysts so typical of this disease are composed of free fungi with only a few phagocytes and fibrin strands The whole "tumor" is surrounded by a thin inflammatory and granulomatous wall


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MYCOLOGY

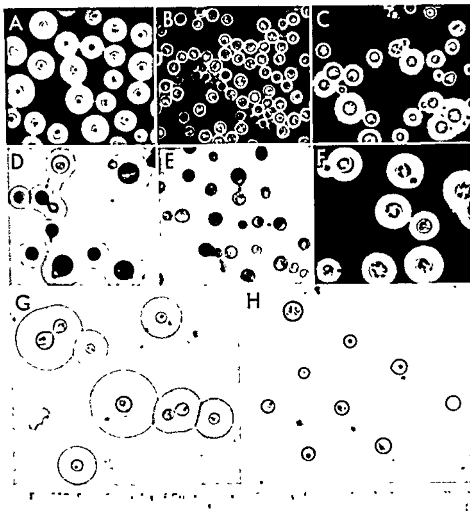
A single species of fungus, Cryptococcus neoformans, is responsible for cryptococcosis. A great many synonyms have been recorded in the literature, and two have been extensively used, Torula histolytica and Cryptococcus hominis. The generic name Torula is botanically inexact. As has been pointed out, it is no longer believed that the organism produces a histolytic toxin, a fact rendering this term inappropriate, and neoformans preceded hominis in usage by several years.

C. neoformans exhibits no method of reproduction other than the production of a single bud at a time, which remains attached to the parent cell until nearly mature in size. Occasional cells in cultures will form a lengthened protrusion characteristic of the germinating tube of the spores of filamentous fungi; such attempts are soon abortive.

1. Direct microscopic examination.—Direct microscopic examination of material obtained from cutaneous lesions or aspirated from the deeper "gelatinous masses" may reveal huge numbers of free, characteristic, thick-walled oval or spherical structures, 6 to 20 microns in diameter, some of which possess single, thin-walled daughter buds in various stages of development. Surrounding many of these cells is a capsule, frequently considerably thicker than the cells themselves The capsule is so translucent as to be almost invisible under ordinary lighting; it may be in evidence, however, owing to its keeping all other cells and debris from approaching the spherule contained within. Thus, the fungus cells appear to be centrally located in clear spaces. This effect is heightened by mixing India ink with the suspected material and examining immediately under subdued light. Spinal fluid should be treated similarly after centrifugation

2. Cultural characteristics.—C. neoformans is usually recovered easily but grows slowly on Sabouraud's glucose agar at room temperature, it is well to utilize blood agar and incubation at 37 C. to prevent failures. On all media, yeastlike mucoid colonies develop, white at first and becoming creamy-yellow to orange-brown with age. Microscopic examination of portions of young colonies reveals the typical singly budding thick-walled spherules, most of them without capsules The buds of some cells become elongated to as much as 30 microns and are seen as slender tubes resembling abortive hyphae, thus revealing the fungous nature of the organism In contrast to the true yeasts, C. neoformans never produces asci or ascospores In older cultures, many of the cells exhibit the typical capsules as previously described. Nonpathogenic Cryptococci usually fail to grow at 37 C

3 Animal inoculation —Mice should be injected intraperitoneally with suspected material Death ensues in from one to four weeks, and gelatinous lesions will be found in the mesentery, in the lymph nodes, and usually in the brain. It is also well to test the pathogenicity of Cryptococci recovered in culture by similar animal inoculation



Serologic demonstration of capsules of Cryptococcus cells from spinal fluid. G, Cryptococ- [illegible]

them from lymphocytes (*Courtesy of Dr James M Neill*)

IMMUNOLOGY

In most cases of cryptococcosis there has been no evidence that the human body was resisting the progress of the disease by any immunologic process. The large, gelatinous cysts with practically no cellular reaction in or about them are striking examples of lack of resistance by phagocytosis. The literature contains a few reports of positive reactions to intradermal injection of extracts of cultures from cryptococcosis ("torulin") (Berghausen; Kessel and Holtzwart). Several authors have reported inability to obtain any reaction to complement fixation and agglutination tests, but Rappaport and Kaplan reported moderately positive responses. Evans and Mehl have isolated and purified polysaccharides from three types of the the fungus, designated as A, B, and C, and have utilized them in precipitin and agglutination tests and in capsular reactions, concluding that the capsule is concerned in such type specificity. Kligman could not demonstrate a serologic response or dermal reactivity in infected rabbits or mice with any of several preparations. Fisher attributed the usual fatal termination of cryptococcosis to poor antibody response and inefficient phagocytosis on the part of the host and to the protection afforded the fungus by its capsule. *Several attempts to utilize vaccines in treatment have been unsuccessful* This is not surprising, in view of similar lack of success with vaccines derived from more antigenic fungi.

DIFFERENTIAL DIAGNOSIS

Pulmonary cryptococcosis must be differentiated from tuberculosis, neoplasm, actinomycosis, coccidioidomycosis, North American blastomycosis, histoplasmosis, and moniliasis. In the central nervous system, the disease is most frequently confused with neoplasm, tuberculous meningitis, encephalitis, or brain abscess. Other deep mycoses and bacterial infections will sometimes need to be considered. Occasionally, even psychotic changes will eventually prove to be due to cryptococcosis

PROGNOSIS

It is likely that many cases of cryptococcosis of the lungs or skin have resulted in spontaneous complete healing without recognition; a few such examples have been recorded The diagnosis is seldom made, however, unless severe involvement is present, and the prognosis is thus usually poor. Whenever central nervous system involvement has been diagnosed, death has followed, usually within a few months but occasionally only after one or more remissions covering a few years In a few instances partially healed cryptococcic foci have been discovered in the brain tissue of persons who have died of unrelated causes

TREATMENT

There is no treatment which can be relied upon to exert more than a [illegible]

of cures Localized cutaneous or mucous membrane lesions and accessible abscesses or gelatinous cysts may respond to incision and drainage or to excision or amputation of an involved limb, especially if assisted by the administration of iodide in large doses and perhaps by X radiation, but a long period of observation is necessary before cure can be assumed.

Basing their theory upon the observation that cultures of C. neoformans do not survive temperatures of 105 to 107 F. for more than six or seven days, several authors have suggested that artificial fever therapy might be beneficial. There has not been sufficient clinical trial of this approach to furnish proof of its value Evidence tending to be discouraging are the facts that rabbits (which have a high normal temperature) succumb to the infection and that febrile patients die more rapidly than afebrile ones Mosberg and Alvarez-De Choudens advocated combining fever therapy with "alkalinization"

Until better methods are available, a high caloric, high protein diet, supplemental vitamins especially of the B series, bed rest, and avoidance of steroid hormones are recommended.

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2 SYMPTOMS —The lungs may become primarily involved The course may be acute or chronic. Acute bronchopneumonia is simulated in the first instance and tuberculosis in the second According to Jacobson, hemoptysis is commonly associated with this infection. There is less emaciation than with pulmonary tuberculosis of similar involvement. The recovery of a species of Aspergillus from lesions on the skin may be significant, but careful controls and experiments are required, since the organism is notoriously a secondary invader.

3 DIFFERENTIAL DIAGNOSIS —If the lungs are infected, the chief disease to be differentiated is tuberculosis. Repeated failure to isolate tubercle bacilli, freedom of the apices of the lungs as seen by roentgen study, atypical onset and course, and at times a history of exposure all favor the diagnosis of mycotic infection. Infection with C. albicans may be readily differentiated by microscopic and cultural studies. Before making a diagnosis of probable aspergillosis, one must exclude other diseases and must repeatedly isolate the microorganism in massive quantities. Aspergilli may be cultured from normal sputum

4. PROGNOSIS —*The course of the disorder may be prolonged.*

5. TREATMENT.—(*a*) The origin of the infection should be ascertained if possible, and the patient may be advised to change his environment or occupation in order to escape further exposure. A gauze mask should be worn by grain threshers if they are susceptible.

(*b*) If tuberculosis can be definitely excluded, potassium iodide should be employed in ascending dosage.

(*c*) Bed rest, wholesome food, and fresh air are advisable.

CONIOSPORIOSIS

Towey and collaborators reported bronchial asthma due to the inhalation of spores of Coniosporum corticale This fungus was present in rotted maple bark.

GEOTRICHOSIS

Symptoms described as due to species of Geotrichum include oral, intestinal, bronchial, and pulmonary manifestations. The mouth lesions are said to be similar to thrush, and only a laboratory study will distinguish the two disorders Colitis has been described as due to a species of Geotrichum. In the bronchial form, a persistent cough and the presence of a mucoid sputum are noted. In the pulmonary form, tuberculosis is simulated, with cavitation and hemoptysis reported as not uncommon. This form may be confused also with blastomycosis For this reason a careful bacteriologic and mycologic study should precede therapy. Treatment of the oral form is similar to that of moniliasis If one is satisfied that tuberculosis can be excluded, the pulmonary form is said to respond to therapy

34. Unusual Systemic Fungous Infections

THERE is considerable doubt as to whether the molds referred to in this chapter ever produce disease without some antecedent preparation. As such, these ever-present fungi are highly selective pathogens. Many of the reports incriminating them as pathogenic leave much to be desired in regard to proof that they are anything more than passive agents Certainly, proof of pathogenicity depends on more than culture from a casual specimen It is significant that few reports in the literature claiming pathogenicity emanate from recognized mycology laboratories or are authored by reputable workers in the field. Fungous disease should be searched for and the effort may be rewarding in instances of obscure symptoms and perplexing physical signs Particularly in cases of lowered resistance in patients with a blood dyscrasia, with a lymphoblastoma, or with diabetes mellitus, saprophytic molds may be capable of invasion of human tissue It should be kept in mind, however, that other causes must be sought and that one should not be content with a diagnosis of mycosis but should recognize the underlying and probably more important disease

ASPERGILLOSIS

Aspergillosis is an uncommon and ill-defined disorder which usually affects the lungs. It is due to one or more species of Aspergillus

1. Etiology —In our routine work we commonly isolate by accident one of many species of Aspergillus The assumption is that this genus is widespread in nature Thom and Church were able to collect 78 different species Aspergillus fumigatus has been isolated more frequently from diseased tissue than any other species, and the consensus is that it may be pathogenic Pigeons, parrots, and other birds are vulnerable and may be the medium of exposure Bird fanciers, grain handlers, and wheat threshers are said to be prone to the infection In a group of cases reported by Sayers and Meriwether, A fumigatus and A. niger were thought to be the cause of a lung infection simulating miliary tuberculosis.

35. Immunology and Allergic Reactions in the Deep Mycoses

THE allergic and serologic changes which occur during the course of deep mycotic infections have been studied by many investigators with highly varying results. The many inconsistencies in their reports make it impossible at this time to present the subject conclusively in generalities applicable to the deep mycoses as an integral group In this volume, therefore, each chapter devoted to one of these diseases contains paragraphs outlining our present knowledge of its allergic and serologic manifestations.

It is permissible, however, to state at this time that there are indications that these diseases may all behave fundamentally in the same manner It is becoming increasingly evident that many, if not indeed all, of the discrepancies heretofore emphasized may be logically ascribed to the fact that the various diseases have not as yet been placed in true apposition while being compared

One of the greatest of the faults has been that the various investigators have prepared their "antigens" for testing in so many different ways that they could not possibly have been more than remotely similar. For example, the complement fixation reaction titer in coccidioidomycosis appears to be closely correlated with the extent of the disease in a manner highly valuable in estimating prognosis This reaction, however, requires an antigen which has been gently treated, since its power to participate can be removed by heating, drying, or any of several known chemical reactions How reliably, then, can we conclude that complement fixation testing is of no value in sporotrichosis from the reports of an observer who prepares his antigen by autoclaving it, drying it over calcium chloride for weeks, or extracting it repeatedly with alcohol to prepare a "pure polysaccharide"? This is but one of many examples in which it is obvious that the same conditions are not being enforced in a manner allowing accurate compari-

with potassium iodide in ascending dosage (*see* dosage chart for sporotrichosis, p. 285).

MUCORMYCOSIS

In the few reported cases of mucormycosis, the lungs are usually the first site to be affected, but an infected eye may be the portal of entry. Acute lobular pneumonia with metastasis to the brain was reported in a 3-year-old child by Baker and Severance. Ulcerative colitis has also been observed. The course of the disease is rapid and death is usual within a few days. In almost all instances the patient has uncontrolled diabetes mellitus. According to Conant *et al.*, none of the reported instances of infection have been verified by culture. Therapy has not been effective.

PENICILLIOSIS

Pulmonary and urinary tract infections have been reported. Great care must be exercised to rule out tuberculosis, as well as other infections and diseases, particularly carcinoma.

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36. Fungous Diseases and Workmen's Compensation

AN ACCURATE (cultural) diagnosis of fungous disease or adequate proof that such a disease is not present may be of special importance to patients who apply for help under one of the state laws on workmen's compensation If a mycotic disease is contracted while he is at work, the worker is entitled to compensation. The hands are the usual site of the rash There is no good evidence that contact dermatitis predisposes to the invasion of fungi Fungi certainly would not from choice select inflammatory tissue such as an eczematous patch. The dermatophytes prefer noninflammatory tissue However, we have frequently observed that an acute tinea may be followed by increased susceptibility to sensitizing and irritating agents, expressed as an eczematous eruption, often supervening on and becoming more serious than the original fungous disease

Lane classified fungous diseases of employees who are examined for industrial disability as follows

1. Primary mycotic infection due to poor working conditions or contact with an infected fellow worker.
2. Exacerbation of a previous mycotic infection due to working conditions.
3. Fungous infection superimposed on industrial dermatitis
4. Industrial dermatitis following fungous infection
5. Mycotic infection bearing no relation to occupation

PRIMARY TRICHOPHYTOSIS OF THE HANDS

Sometimes the patient's work may be directly responsible For instance, the occurrence in a bank teller suggests an occupational origin, since handling of paper money may be the source A fellow worker who has the disease may be the important focus The diagnosis of primary dermatophytosis of the hands should not be based solely on clinical grounds but should be verified by microscopic and cultural studies. Each case presents an indi-

sons to be made. It seems significant that in several instances in which the necessary criteria for comparison have been fulfilled the reactions have been much more nearly similar.

It is apparent that other discrepancies can be explained on the basis that the two diseases being compared were not in the same stage or form at the time of comparison. For example, the recent trend toward acceptance of the concept that primary cutaneous inoculation of a deep mycosis results in a self-limited chancriform syndrome rather than a chronic dangerous disseminated skin infection indicates that sporotrichosis and blastomycosis have usually not been compared while in the same stage or type. Under the circumstances it would indeed be astonishing if the same serologic or allergic responses were obtained.

At present it seems not too fantastic to anticipate that most of these discrepancies can be resolved by further study and interpretation, which will eventually furnish reliable testing procedures of diagnostic and prognostic significance In addition, valuable clues will undoubtedly appear, leading to a better understanding of the immunology of these diseases and finally, perhaps, to their control by such procedures. Such clues may then prove valuable in researches into the immunology of the much more prevalent bacterial scourges of mankind, such as tuberculosis and leprosy, whose complicated immunology has as yet defied scientific investigation.

Perhaps a series of testing procedures can be developed for each disease which will be of as much value to clinicians as are those for coccidioidomycosis, such as the complement fixation reaction, the precipitin reaction, and the delayed tuberculin type of response to intracutaneous inoculation of coccidioidin In this disease these reactions appear to be closely related to the immunologic status of the patient and are of inestimable value in diagnosis and prognosis.

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37. Fundamentals of Elementary Mycology

FUNGI are members of the Thallophyta, one of the four major divisions of the plant kingdom. The Thallophyta are characterized by having their vegetative plant body undifferentiated into *roots, stems,* and *leaves,* in contrast to higher plants Such an undifferentiated plant body is termed a *thallus.* The phylum Thallophyta comprises the Algae, containing chlorophyll and capable of synthesizing their own food from carbon dioxide and water with the aid of sunlight, and the Fungi, without chlorophyll and therefore unable to synthesize their own carbohydrate foods. Fungi are thus dependent organisms and must obtain their food from organic matter synthesized by other organisms. If they obtain their nourishment at the expense of living organisms they are termed *parasites,* if from dead organic material they are called *saprophytes*

In general, the vegetative thall[illegible]

[illegible] of loosely connected cells [illegible] may grow as one-celled or budding organisms for a time, or in a particular environment, and produce abundant mycelium under changed conditions. Many of the fungi pathogenic to man and animals show this *dimorphism,* developing in a yeastlike form in tissues and forming mycelium in culture This phenomenon is not observed in species pathogenic for plants

The hypha originates from a spore by the formation of a *germ tube* According to the thickness and nature of the spore wall, one or more germ tubes push their way through the spore wall at any point or through visible thin places known as *germ pores*

The contents of the spore pass into the germ tube, which elongates into

vidual problem, and it is important at least to attempt to trace the origin of the proved infection. In this way additional proof is gained of the occupational or nonoccupational origin of the infection, and prevention of further spread may be obtained. In many instances, taking an accurate history will reveal other causes. While the diagnosis of primary fungous infection of the hands is probably too frequent, the disease should not be overlooked.

DERMATOPHYTID SECONDARY TO A FUNGOUS FOCUS

The criteria for the diagnosis of dermatophytid are given in another part of the book. This diagnosis should never be made from clinical inspection alone. There must be a fungous focus elsewhere, a positive reaction to trichophytin, and a reasonable certainty of exclusion of all other possible cutaneous disorders, particularly dermatitis venenata.

THE RARE MYCOSES

Such infections as sporotrichosis may be of occupational origin, as in gardeners. Pulmonary moniliasis and aspergillosis in grain handlers have been reported

NONMYCOTIC DISEASE

There are numerous dermatoses which may appear on the hands A negative reaction to the intracutaneous trichophytin test will exclude dermatophytid. It is beyond the province of this work to discuss further the differential diagnosis of eczematous eruptions of the hand, such as dermatitis venenata, neurodermatitis, pompholyx, acrodermatitis, and pustular psoriasis.

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stance peculiar to fungi is *volutin*, which may appear as granules or vacuoles. It is claimed that volutin is free nucleic acid. Streaming of the cytoplasm is evident in many of the coenocytic Phycomycetes.

Many fungi exhibit pigment in their hyphae, spores, or both, the nature and degree of which may depend on the age of the culture and the temperature and chemical composition of the medium. Some fungi, although containing no color in the mycelium or spores, produce a soluble pigment which diffuses into the substratum on which they are growing.

When the majority of fungi have produced an abundant vegetative mycelium and have accumulated a sufficient food reserve, reproductive structures (spores) are developed on the mycelium. Spores may be defined as characteristically formed cells or groups of cells which separate from the mother plant and are capable of developing into new individuals. Fungus spores function as organs of propagation, multiplication, and dispersal or as organs for resisting unfavorable conditions of environment.

TYPES OF FUNGI

The fungi are divided into four large groups on the basis of the nature of their mycelium and type of sporulation.

1 PHYCOMYCETES —These fungi usually possess an abundant branched, nonseptate, multinucleate, tubular mycelium Usually, septa or cross walls are formed in the mycelium only when spore-bearing bodies or sex organs are being produced. Cross walls are sometimes formed also in very old mycelium and are common to a few types These exceptions may make positive identification difficult unless spore-bearing structures are present The most characteristic feature of the Phycomycetes is the formation of asexual spores in *sporangia* by *cleavage planes* No other fungi form spores in this manner.

2 ASCOMYCETES —The mycelium of most Ascomycetes is abundant, richly branched, and regularly septate but may be reduced to single budding cells or chains of budding cells, as in the true yeasts All Ascomycetes at some time in their life history produce sexual spores inside of a spore mother cell, termed *an ascus* They usually also produce many types of asexual spores

3 BASIDIOMYCETES —The Basidiomycetes possess septate, much-branched mycelium which frequently has *clamp connections* between the cells The primary mycelium has uninucleate cells which later become binucleate by the *anastomosis* of vegetative cells

The Basidiomycetes often produce large fruiting bodies of various forms, such as the mushrooms and puff balls The rusts and smuts which are parasitic on plants belong to this group The fruiting bodies of several Basidiomycetes are poisonous when eaten The most important characteristic of this group is the *basidium*, a spore mother cell producing its spores externally

a hypha with continued growth at the apex. Branching usually follows by protrusion of new growing points from the sides of the hypha until a mycelium is formed. Cross walls, or *septa*, are formed by the deposition of cell wall material as annular thickenings, beginning at the outside and gradually spreading across the hyphae. During rapid growth the formation of cross walls may be delayed, to be followed later by simultaneous or successive development of many septa. Frequently these septa are pierced by one or more openings through which a continuity of protoplasm from cell to cell may be established.

In some fungi, notably the Phycomycetes, septa are lacking, and the whole vegetative thallus is one large, branched, multinucleated cell This type of mycelium is said to be *coenocytic* and permits unrestricted flowing of the protoplasm throughout the entire vegetative thallus.

The mycelium of many fungi may be differentiated into an absorbing or attachment portion and a vegetative portion. In some cases the absorbing portion assumes the nature of branched and tapering rootlike filaments known as *rhizoids*. Many fungi parasitic on higher plants do not kill their host cells, but possess specialized knoblike or coarsely branched absorbing organs known as *haustoria*, which penetrate the cell wall and absorb nourishment directly from the host's cytoplasm.

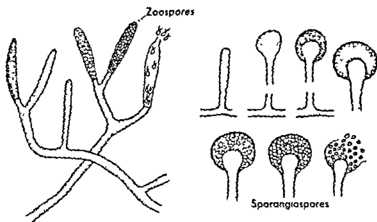
In the development of fruiting structures, such as a mushroom, the hyphae grow together in groups and intertwine to form a fleshy or hard tissue called *plectenchyma*. In other cases the hyphae lose their individuality, and their cells form compact masses of rounded or polygonal cells. Such a tissue is known as *pseudoparenchyma* and is frequently encountered in *sclerotia* Sclerotia are resting bodies formed chiefly of parenchyma tissue which has become dry and firm. These bodies have the property of remaining viable over long periods in an unfavorable environment and with the return of favorable conditions germinate to form normal mycelium

The cells of fungi are similar to those of higher plants in their general characteristics The cell wall is of variable thickness and composition In many of the Phycomycetes and yeasts the cell wall consists largely of pure cellulose In the majority of the higher fungi, however, it is composed of chitin, fatty acids, and carbohydrates Calcium carbonate and various other salts are frequently deposited on or in the cell wall.

The *protoplast* consists of one or more nuclei surrounded by granular or vacuolated cytoplasm The nuclei of most fungi are very small and not easily demonstrated The nature of the cytoplasm varies with the age of the cells and the amount of reserve substances contained, among which are a number of carbohydrates, fats, oils, and proteins Fats appear in the form of very refractile globules and may be easily identified by staining with Sudan III. Some confusion has arisen because of mycologists' mistaking these fat globules for *endospores* Carbohydrate is usually stored as glycogen, which is readily transformed to sugars. Another reserve sub-

Sporangiospores are formed in large numbers and released by rupture of the thin sporangial wall. Sporangia are usually borne on a stalk known as a *sporangiophore*, which may be simple or branched Motile spores borne in sporangia are known as *zoospores* and are produced by many species of water molds. The Phycomycetes characteristically produce their asexual spores in sporangia.

Conidia are thin-walled, single-celled, or multicellular spores usually borne at the end of a specialized hyphal branch. They are delimited by being abstricted and may be considered as modified vegetative units. The hyphae which give rise to conidia are in most cases modified and differentiated from the vegetative hyphae and are termed *conidiophores*. Conidio-



Development of zoospores and sporangiospores of Phycomycetes.

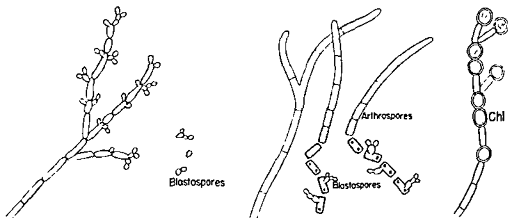
phores may be simple or characteristically and elaborately branched or modified Conidia may be formed on the conidiophore either singly, in heads or in chains When the conidia are in chains they may be abstricted singly from the conidiophore and shoved upward or they may bud off one another Many fungi produce conidia of two sizes, small unicellular *microconidia* and larger frequently several-celled *macroconidia* Some conidia are borne directly on the mycelium and are said to be sessile, as in Trichophyton, others may be borne on very short sterigmata, as in Sporotrichum

Conidiophores may arise directly from the mycelium or from a compact mass of modified hyphal cells known as a stroma. They may be free, aggregated, or enclosed in a fruit body composed of sterile vegetative cells. When the conidiophores are enclosed as a lining in the bottom of an enclosed fruit body, the fructification is known as a *pycnidium* If the conidiophores are elongated and closely aggregated in a fascicle, the fruiting body is termed a *coremium* Sometimes the conidiophores may be short and closely aggregated on a cushion-like *stroma*, forming a *sporodochium* or *tubercle*. Sporodochia with very thin stromatic bases are known as *acervuli*

4. Fungi imperfecti.—The sexual stage of a fungus is considered the *perfect stage*, while the asexual stage is known as the *imperfect stage*. Many fungi either have lost their ability to form the sexual stage or this stage is unknown. These fungi reproduce only asexually and are grouped together under the name of Fungi imperfecti. Most of the fungi pathogenic to man and those frequently encountered as contaminants in the laboratory belong to this group.

REPRODUCTION

Fungi reproduce by many types of spores which are developed in different ways. The simplest type is the *thallospore*, which is developed



directly from the vegetative thallus. Three kinds of thallospores are encountered, *blastospores*, *arthrospores*, and *chlamydospores*.

Blastospores are spores formed as buds which are abstricted either from a single cell, as in the yeasts and yeastlike fungi, or laterally from a mycelium or pseudomycelium

Arthrospores are formed by the disarticulation of short vegetative cells of the hyphae without change in the cell wall or in shape.

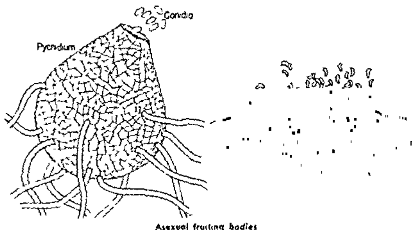
Chlamydospores are formed by the rounding up and thickening walls of the vegetative cells of the hyphae They may be intercalary in the hyphae or terminal on short lateral stalks Such thick-walled resting spores remain intact and viable after the remainder of the mycelium has disintegrated

Asexual spores are developed in abundance in or on specialized spore-forming structures Three common types of asexual spores will be discerned: *sporangiospores*, *zoospores*, and *conidia*

Sporangiospores are nonmotile spores produced in a closed swollen structure, the sporangium, developed from a modified branch of the vegetative hyphae The spores are delimited by cleavage planes progressing inwardly from the periphery of the dense cytoplasm of the sporangium

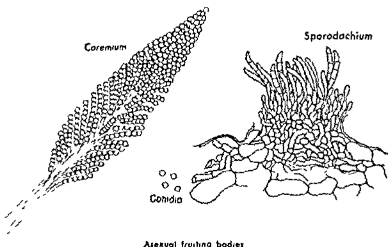
sexual reproduction In the Oomycetes the gametes are quite dissimilar and are produced in distinctly different gametangia, while in the Zygomycetes the gametes are similar and there is no essential difference between the gametangia.

In a representative Oomycete a large spherical female sex organ, the



Asexual fruiting bodies

oogonium, containing one or more eggs, arises as a side branch from the vegetative mycelium and at maturity is cut off from the hypha by a cross wall. A male sex organ, the *antheridium* arises from the same or different mycelial branch and makes contact with the oogonium A *fertilization tube*

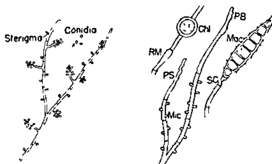


Asexual fruiting bodies

from the antheridium penetrates the oogonial wall and the male nucleus is discharged directly into the egg No motile sperms are produced After fertilization a thick wall forms around the *Zygote* and it becomes a resting

Conidial production

Sexual spores of fungi are produced as a result of a nuclear fusion and a meiosis of a spore mother cell. Well-defined sex organs and gametes are *found in relatively few fungi (Phycomycetes).* The nature of the spore mother cell and the development of the sexual spores are important in

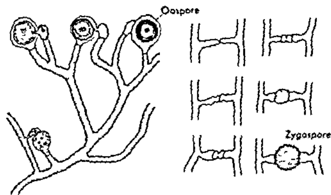


Conidial production

classification Hyphal fusions frequently occur, but mere fusion of cells is not indicative of sexuality, as there must be a nuclear fusion followed by a reduction division when spores are produced.

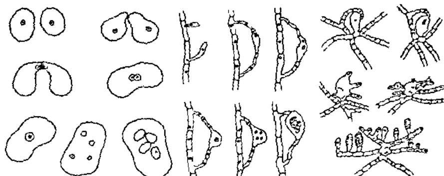
1. SEXUAL SPORES OF PHYCOMYCETES —The Phycomycetes are divided into two groups, *Oomycetes* and *Zygomycetes*, on the basis of their

the ascogenous hyphae is binucleate. Further buds arise from the ascogenous hyphae and become modified into asci. The young asci are binucleate, but the nuclei soon fuse, forming a spore mother cell with a single diploid nucleus, which undergoes reduction cell division to form four haploid nuclei, and these in a majority of cases divide again by mitosis.



Development of sexual spores of Phycomycetes.

A part of the cytoplasm of the ascus gathers around each nucleus and is soon set off from the remaining cytoplasm by a cell wall, forming an ascospore. The spores are thus formed by *free cell formation* No cleavage planes similar to those found in the sporangia of Phycomycetes are ever



Development of asci and ascospores

found. The young primary spore may become divided into several cells, so that the mature spore is multicellular All young asci, regardless of how they originate, are at first binucleate, with two haploid nuclei which fuse to form a diploid nucleus, which in turn undergoes meiosis to form four haploid nuclei The ascus is thus a true spore *mother cell*

The more simplified Ascomycetes produce the asci free on the vegetative mycelium, but the higher forms have the asci born in a fruiting body, or *ascocarp* The ascocarp is composed of vegetative hyphae which are

oospore. After a rest period the oospore may germinate and the contents emerge as zoospores, which swim for a time, come to rest on a suitable substrate, and develop into a mycelium.

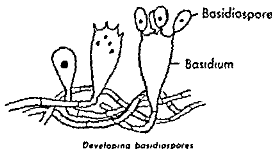
In a representative Zygomycete, such as the bread mold fungus, Rhizopus nigricans, when two hyphae of different sexual strains come into contact, a short single branch, termed a *progamete,* is produced from each hypha near the point of contact. The progametes elongate until their ends touch. The terminal portion of each progamete then becomes swollen and is cut off from the basal portion by a cross wall. These swollen multinucleate cells are termed *gametangia,* and the basal portions of the progamete are known as suspensors. The wall between the gametangia is dissolved, and their contents fuse to form a zygote. The zygote enlarges, develops a thick rough wall, and is filled with an abundance of reserve foods The mature zygote is known as a *zygospore* and remains viable for a long period.

2 SEXUAL SPORES OF ASCOMYCETES.—The definitive spore of the Ascomycetes is a sexual spore termed an *ascospore.* These spores are formed as the result of a reduction cell division in a spore mother cell called the ascus. The ascospores are formed by free cell formation within the ascus and are not developed by cleavage like the sporangiospores of the Phycomycetes. The ascus always arises as a result of a nuclear fusion and in its early stage contains a single diploid nucleus which give rise to the primary ascospore nuclei by reduction cell division (*meiosis*). The ascus with its diploid nucleus may arise in a number of ways. The simplest method of ascus formation is by the conjugation of two haploid unicellular plants, as seen in some of the yeasts. In this case two neighboring yeast cells push out protuberences which touch and fuse. An opening forms between the two cells, and the nucleus from one cell moves into the adjacent cell and fuses with its nucleus This diploid cell, or zygote, is transformed directly into an ascus, where, after meiosis, four haploid ascospores are formed.

Among some of the simple Ascomycetes possessing a true mycelium, sexual reproduction is also by conjugation, as in the genus Endomyces Here two hyphal branches come in contact, the adjacent tip cells unite, and the nucleus from one cell passes into the other cell and unites with its nucleus. The cell containing the diploid nucleus enlarges and becomes an ascus with four ascospores

In the majority of the higher Ascomycetes, the sex organs are not distinct and are seldom observed in culture. They arise from the vegetative mycelium and are usually differentiated by a swollen filament, representing the oogonium, and a slender filament, the antheridium, which frequently curls about the oogonium A male nucleus enters the oogonium, which now becomes binucleate The nuclei do not fuse but divide simultaneously so that several pairs of nuclei are found in the oogonium Later, buds arise from the oogonium and grow into septate branching filaments known as *ascogenous hyphae* Pairs of nuclei move into the buds, so that each cell of

basidium and then undergo reduction cell division, giving rise to four haploid nuclei. Four tiny projections, *sterigmata*, next appear on the apex of the basidium, on the tips of which small buds arise. The four nuclei in the basidium pass into the buds, which enlarge and become basidiospores.

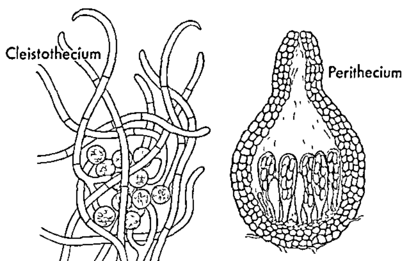


Developing basidiospores

When ripe the *basidiospores* are abstricted from the basidium and become dispersed. The basidium is similar to the ascus except that the spores are produced outside rather than inside. They are both spore mother cells, and the spores are the result of a nuclear fusion and a reduction cell division.

often modified into tissues serving as a protective covering. This covering may be a few loose floccose filaments surrounding a few scattered asci, as in *Ctenomyces*. In Aspergillus the fruiting body is a spherical closed structure with a wall of compact and thickened collenchyma-like cells. This entirely closed fruiting body with its scattered asci is known as a *cleistothecium*.

A second type of ascocarp is the *perithecium*, which is common to the majority of Ascomycetes. The perithecium is a closed, flask-shaped fruit



Sexual fruiting bodies of Ascomycetes

body having a definite opening, the *ostiole*, with the asci arranged in a parallel series. The ostiole may be a simple pore or may be elongated into a definite neck

The third type of ascocarp is the *apothecium* This is an open disk or cup-shaped fruit body, having the asci arranged in a parallel series. Apothecia are usually fleshy, while perithecia are leathery or hard and carbonaceous The type of ascocarp is used in separating the Ascomycetes into definite taxonomic groups

3 SEXUAL SPORES OF BASIDIOMYCETES —Definite sex organs are absent in the Basidiomycetes, however, we find that the cells of the mycelium in the fruiting bodies become binucleate On germination of the spores, the primary mycelium has uninucleate haploid cells, but after considerable growth the cells become binucleate This condition is made possible by the anastomosis of two pieces of mycelium and the continued growth with two haploid nuclei in each cell In the fruit body of a mushroom, the cells making up the center of the *gills* are binucleate cells Some of the mycelium turns outward and forms a fruiting layer on the outside of the gill The tip ends of the hyphae become swollen and club shaped, forming spore mother cells known as *basidia* The two nuclei fuse in the young

too high. It should be kept in mind that, while a vaccine test may elicit a specific reaction, it may nevertheless mean nothing in relation to the problem at hand. This situation is exemplified in the histoplasmin test. Current thought indicates that histoplasmosis is a common and comparatively benign infection. The hilar nodes become involved but the disease commonly burns out spontaneously, leaving only roentgen evidence of the invasion. The histoplasmin test, however, remains positive, sometimes for years In Coccidioides infection, the skin test is helpful in investigation of an individual case or in mass surveys, since a negative reaction rules out the disease. It is also of great help from the prognostic standpoint in the management of patients seriously ill with the disease.

Roentgen examination of the lungs has been mentioned in regard to histoplasmosis. The findings by X rays may give the first clue to the nature of the pathologic process, not only in this disease but in blastomycosis and in coccidioidomycosis The base of the lung is usually affected in preference to the apex, cavitation is less common than in tuberculosis Metastatic growths in the bony framework or internal organs may be detected by means of the roentgen rays

Histologic examination reveals the nature of the reaction of the host to the invasion of the pathogenic microorganisms The fungi themselves are rarely seen. In the superficial chronic infections the lack of pathologic changes may be helpful in differentiation from other dermatoses In the deep forms of infection, there is no specific picture and granulomatous changes are the rule. Moore showed the close similarity between tuberculosis and many of the deep invasive fungous infections. In the acute form of each, a highly inflammatory reaction occurs, often leading to abscess formation. In the chronic forms, there are granulomas containing giant cells arranged in tubercle-like formation and plasma, epithelioid, lymphoid, and polymorphonuclear cells In fungous disease there are usually fewer epithelioid cells and more plasma and polymorphonuclear cells than in tuberculosis

When the diagnosis cannot be definitely established but the clinical features point to a fungous disease, it may be considered expedient to institute therapy. Improvement of the disorder following fungicidal therapy is evidence that the disease is mycotic. Unless the patient is seriously ill or there is other urgent reason, a therapeutic test is hard to justify It is more logical to delay active therapy until the diagnosis is established by recognized laboratory methods This may necessitate a few days of placebo therapy

Recovery of a recognized pathogen from a characteristic lesion is sufficient to establish the organism as the cause of the infection. If the lesion is atypical, particularly if the isolated fungus is of a variety not usually pathogenic or not usually isolated, further proof of pathogenicity is ordinarily required. The use of animals may be instructive but is not in itself conclusive, since variation in susceptibility with the species of animal

38. Methods of Diagnosis

As IN any branch of medicine, the basic requisite in diagnosis is clinical knowledge and clinical acumen. Without these, there will be no suspicion of a mycosis and consequently no investigation, or, conversely, the patient will be subjected to needless and perhaps meddlesome tests or procedures. With study and experience, the clinical features of the mycoses are often found to be distinctive and at least the diagnosis will be correctly considered as a differential alternative.

It may again be emphasized that there should be a close association between the clinician and the laboratory so far as mycologic disorders are concerned. It is almost always desirable to substantiate the clinical impression by appropriate laboratory tests, which are considered in detail in the next chapter.

In both the superficial and the deep mycoses, demonstration of the causative organism in a direct mount or by culture is recognized as the most satisfactory laboratory procedure. Once the pathogenic fungus has been demonstrated, other tests are helpful to indicate patient resistance and extent of the disease and to assist in the evaluation of therapy.

In patients suspected of a mycotic infection of the scalp, the examination of the scalp in filtered ultraviolet rays may reveal typical fluorescence and substantiate the clinical findings Even in this case, a cultural diagnosis is highly desirable, since the prognosis varies considerably with the infecting microorganism. It should be reiterated that certain fungi may invade the hair follicle and not initiate fluorescence, so that blind dependence on the Wood light as a certain test for tinea of the scalp may result in an important error in diagnosis

Allergic reactions induced by appropriate vaccines are sometimes helpful in both superficial and systemic mycoses The subject as it relates to the dermatophytes is considered in detail in Chapter 24 A positive reaction to the trichophytin test is requisite for a diagnosis of dermatophytid. A negative reaction to trichophytin will therefore rule out this diagnosis when it is being considered Oidiomycin is completely useless in the diagnosis of moniliasis, as the number of false negative and false positive reactions is

too high. It should be kept in mind that, while a vaccine test may elicit a specific reaction, it may nevertheless mean nothing in relation to the problem at hand This situation is exemplified in the histoplasmin test. Current thought indicates that histoplasmosis is a common and comparatively benign infection. The hilar nodes become involved but the disease commonly burns out spontaneously, leaving only roentgen evidence of the invasion. The histoplasmin test, however, remains positive, sometimes for years. In Coccidioides infection, the skin test is helpful in investigation of an individual case or in mass surveys, since a negative reaction rules out the disease. It is also of great help from the prognostic standpoint in the management of patients seriously ill with the disease.

Roentgen examination of the lungs has been mentioned in regard to histoplasmosis. The findings by X rays may give the first clue to the nature of the pathologic process, not only in this disease but in blastomycosis and in coccidioidomycosis. The base of the lung is usually affected in preference to the apex; cavitation is less common than in tuberculosis Metastatic growths in the bony framework or internal organs may be detected by means of the roentgen rays.

Histologic examination reveals the nature of the reaction of the host to the invasion of the pathogenic microorganisms The fungi themselves are rarely seen In the superficial chronic infections the lack of pathologic changes may be helpful in differentiation from other dermatoses. In the deep forms of infection, there is no specific picture and granulomatous changes are the rule Moore showed the close similarity between tuberculosis and many of the deep invasive fungous infections In the acute form of each, a highly inflammatory reaction occurs, often leading to abscess formation. In the chronic forms, there are granulomas containing giant cells arranged in tubercle-like formation and plasma, epithelioid, lymphoid, and polymorphonuclear cells. In fungous disease there are usually fewer epithelioid cells and more plasma and polymorphonuclear cells than in tuberculosis.

When the diagnosis cannot be definitely established but the clinical features point to a fungous disease, it may be considered expedient to institute therapy. Improvement of the disorder following fungicidal therapy is evidence that the disease is mycotic Unless the patient is seriously ill or there is other urgent reason, a therapeutic test is hard to justify It is more logical to delay active therapy until the diagnosis is established by recognized laboratory methods This may necessitate a few days of placebo therapy.

Recovery of a recognized pathogen from a characteristic lesion is sufficient to establish the organism as the cause of the infection If the lesion is atypical, particularly if the isolated fungus is of a variety not usually pathogenic or not usually isolated, further proof of pathogenicity is ordinarily required The use of animals may be instructive but is not in itself conclusive, since variation in susceptibility with the species of animal

shows that the response in human beings also varies. As mentioned by Weidman and others, the more frequent use of experimental autoinoculation is advisable. It is common knowledge that there is a considerable flora of contaminants, and it is possible that on occasion pathogenic strains may appear among them.

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39. Laboratory Methods

THE procedures for laboratory investigation of mycotic disorders are, on the whole, not difficult to master. The methods outlined here are those which we use daily in our laboratories and in private practice They have been proved by experience to be efficient The media and technique of the mycologist differ somewhat from those of the bacteriologist Since most fungi grow well at room temperature, an incubator is rarely necessary. Moreover, some fungi which grow luxuriantly at room temperature will scarcely develop when incubated at body heat This effect may be in part due to desiccation of the agar (lack of moisture) as well as to unsuitable temperature Culture of bacteria requires incubation in an elevated temperature For this reason bacterial contamination of fungous cultures is rarely seen, although many species of bacteria normally are present in the mouth, scrapings from the tongue on acid dextrose agar incubated at room temperature are singularly and strikingly free from bacterial contamination. The chief contaminants are other fungi, such as Penicillium or Scopulariopsis Elaborate media are not required, and except in detailed work and investigation of minute points, only a few media are necessary unless one is attempting to isolate Actinomyces (closely related to bacteria) or Blastomyces In the former case, incubation at body heat and the use of blood for enrichment may be requisite In addition, some strains grow only under anaerobic conditions Blastomyces dermatitidis usually requires incubation at 37 C , with blood agar for the primary isolation Sometimes growth occurs at room temperature

Another difference between growth of bacteria and growth of fungi on artificial media is partly due to the method of incubation Whereas bacteria multiply and colonization is detectable after a few hours or within a few days, a comparable status with fungi requires from several days to three or four weeks. On the average, seven to 10 days elapse before a definite report of the species of infecting fungus can be delivered

Pathologists are frequently called on to make an unequivocal diagnosis from specimens of tissue taken by biopsy or post mortem This is not always possible There is often a close resemblance between the mycoses

of granulomatous nature and tuberculosis, and if the infecting microorganism is not observed, a definite diagnosis without cultural information may be impossible. As in tuberculosis, the fungous disease may be acute, with abscess formation resulting, or chronic, with the development of giant cells, often in tubercle-like fashion, together with plasma cells, lymphocytes, epithelioid cells, and occasional mast cells.

COLLECTION OF SPECIMENS OF DISEASED TISSUE

The large majority of specimens intended for mycologic examination are derived from the cutaneous surface. These include scales, macerated skin, the roofs of vesicles or bullae, hairs, and pieces of nail. The specimen may consist of pus from deep cutaneous lesions (either open or closed) or from an internal source (such as an appendical abscess). The material may be one of the body fluids, such as blood (for histoplasmosis) or spinal fluid (for cryptococcosis). The sputum usually contains one or more species of fungus. Due care must be exercised in differentiating between the pathogenic and the saprophytic fungi obtained. Study of the oral mucosa (particularly of the tongue) and of the anogenital area (especially in cases of moniliasis) is frequently an integral part of the mycologic examination. Routine examination of a vaginal discharge for fungi is as necessary as for bacteria or protozoa.

The selection of an appropriate spot from which to obtain specimens for direct microscopic examination or cultural implantation is extremely important If the suspected fungous disease presents lesions in various phases of development and degrees of activity, it is wise to select carefully an area obviously recently and actively involved Frequently this is at the "advancing border" of the process If there are several types of lesions, a sample should be obtained from each. Spots which have not been recently medicated should be chosen if possible Since fungi themselves seldom cause much pus, purulent areas are probably highly infected secondarily with bacteria, and it will be difficult to obtain the causative organism from them, it is therefore well to search for areas less involved in this manner or if none are available to treat the lesions for a few days with mildly antibacterial measures before proceeding

In the majority of instances cleaning the selected site with a cotton sponge wet with 70 per cent alcohol will remove enough extraneous debris containing bacteria* and saprophytic fungi so that a pure culture of the pathogenic fungus can be obtained It is almost axiomatic that such treatment will not suffice to remove the pathogen as well, since it is of necessity existing at the deeper portion of the lesion

In contradistinction to bacteria, the distribution of fungi in tissue in

* Bacteria grow poorly in dextrose agar at room temperature and are usually no problem Under tropical conditions or when the specimen is heavily contaminated, a medium to which chloromycetin has been added should be employed

even the severest infections is comparatively sparse, it is therefore necessary to remove reasonably large portions to avoid missing a pathogen. An appropriate instrument to obtain most specimens is the ordinary surgical scalpel A broad-bladed instrument which has become too dull for the purpose for which it was made will suffice for most situations. However, if the indication is for a sharp implement we advise the replaceable-blade scalpel The smallest of the convexly rounded blades (No. 15) should be selected when small-necked bottles containing culture media are used. The first specimen thus obtained should be used for direct microscopic examination; and the next, even deeper, one for cultural implantation, since the latter is less likely to be contaminated. A careless, offhand manner in collecting a few scales or dried crusts from the unwashed skin surface will militate against success.

When a fungous infection of the scalp is suspected, specimens of hairs should be selected while the patient is observed under filtered ultraviolet rays. It should be noted that some types of hair infection do not produce fluorescence. Samples of many hairs may be obtained by scraping across the infected patch with a sharp scalpel. Some workers obtain satisfactory material by extracting solitary hairs with epilating forceps.

In fungous-diseased nails, the hard outer shell when present and the porous, crumbly mass of detritus is unsuited for mycologic examination. Such material should be adequately removed with scalpel or nail clippers, after which the specimen should be obtained from the exposed base

If a mycosis of the lungs is suspected, a specimen of sputum or a fragment of tissue should be obtained bronchoscopically Thus one may determine whether Monilia, Actinomyces, or other organisms which have been noted in a direct smear or in culture from a casual specimen of sputum are actually invading the lung or are merely present in the mouth as saprophytes. Primary fungous disease may be considered probable if the fungous material is found in large amounts or if the same species of fungus is repeatedly isolated while a search for tuberculosis, carcinoma, and other pulmonary diseases remains unrevealing

Occasionally it may be necessary to place a pathologic specimen taken from a patient on a sterile slide or in a sterile container for inoculation into media and examination at a later time, but when possible it is preferable to transfer the material directly from the patient to the culture medium. This eliminates much secondary contamination and saves time and effort It is necessary to select instruments narrow enough to enter the openings of whatever culture flasks, tubes, or bottles are to be used

CARE OF INSTRUMENTS AND GLASSWARE

If sterilization is effected by boiling, the cutting edges of the instruments soon become dulled To prevent this, the instruments after use are immersed in a 10 per cent solution of cresol for at least half an hour They

are then washed in water and placed in a 70 per cent concentration of alcohol (saturated with sodium bicarbonate), where they are left until used. There is no rusting in either solution, and the instruments can be left in either for an indefinite period. The syringe and the needle are sterilized by being placed in boiling water for 10 minutes.

Used slides are first separated from the coverslips; the two are then placed separately in 10 per cent solutions of cresol, which cleans and sterilizes. After a few days they are rinsed in water and dried for use. The same solutions of cresol may be used repeatedly.

Discarded tubes of used mediums may be conveniently sterilized and cleaned in the following manner. With the cotton pledgets in place, the tubes are put in an upright position and left under a steam pressure of 15 pounds for one hour. All growth is thus destroyed. While the agar is still liquid, the pledgets of cotton are removed and the tubes are filled with hot water. The water dilutes the agar so that it cannot again harden, and the contents of the tubes may now be safely discarded into a drain. The tubes require little more than a soaking in a solution of detergent, such as Soilax, and a rinsing in clear water to be ready for use again. With this technique, breakage is reduced.

Petri dishes are best sterilized separately After sterilization, as outlined in the preceding paragraph, they are allowed to cool. The agar is then removed with a spatula and the dishes are washed with soapy water or with a solution of detergent

If any tubes have been sealed with paraffin, cleaning them separately will prevent the filming of other glassware. If wax pencil has been used to label tubes or Petri dishes, it is preferable to remove the marks with benzene as the dishes are discarded and before sterilizing.

THE MICROSCOPE

The microscope is an important instrument in mycologic work A beginner should become familiar with the various parts and learn the few necessary details of its proper care The oil immersion objective is only occasionally necessary, as in the examination of scales from a lesion suspected of being erythrasma The low power objective is useful in locating the most desirable field for examination A trained observer may detect fungi by their appearance under low magnification (approximately × 100) For finer details and for confirmation of the original observation, study of the material under the high dry objective (above × 400) is usually profitable We have found a third objective, giving an intermediate magnification (about × 200), useful for the closer examination of many slides. This has a larger field and a greater depth of focus than the ordinary high dry objective, at this power, identification of structure is readily attained If the preparation is flooded with solvent, some of it is almost certain to run over onto the stage of the microscope. If the slide is then

removed and the stage washed with a damp cloth, no harm will result. Unless the solvent is removed, the stage will become tarnished and discolored. If the objective accidentally touches the solvent, the solution should be wiped off promptly with a wet microscope paper; otherwise vision is interfered with. Only soft lens paper, especially made for the purpose, should be used to clean the lenses in the eyepiece and objective. The beginner often makes the mistake of opening the diaphragm too far, allowing an overabundance of light to pass through. Since the material is usually unstained, the light must be subdued in order that fungous elements may be visible.

PRECAUTIONS AGAINST LABORATORY INFECTIONS

It is important never to leave infected slides or instruments where they may be accidentally handled When they have been used, it is better to dispose of them immediately or to place them in a 10 per cent solution of cresol. The use of rubber gloves may be advisable in theory, but it is seldom carried out in practice The use of soap and water at frequent intervals is sufficient. With most of the dermatophytes there is little danger of inhalation of spores from colonies. For this reason it is not necessary to wear masks when working with them. When one is working with cultures of C immitis, danger of inhalation is real and a mask should be worn; moreover, care should be taken that there is no draft, as from an open window or from a fan, and it is advisable to wet the culture thoroughly with sterile water In dealing with old cultures, it may be incorrectly assumed that when the medium dries, the fungi are dead, they may still be viable and able to cause infections. Floors, table tops and other accessible areas which might be contaminated should be frequently sponged with a 3 per cent solution of cresol followed by the use of soap and water.

The use of a motorized bur to remove infected nail tissue, a procedure which has become popularized, is probably inadvisable, because sterilization of the instrument is difficult and it is impossible to keep the infected nail material, which is pulverized by the rapidly revolving bur, from being disseminated through the air If this method is used, a mask should be worn and newspapers on which the dust has been collected should later be burned.

DIRECT MICROSCOPIC EXAMINATION

The presence of fungous elements can usually be established by direct microscopic examination In many instances this is sufficient to establish the diagnosis. With tinea versicolor and a few other mycoses, caused by organisms which cannot be easily cultured, this is the sole method of confirming the clinical diagnosis A positive result is much more valuable than a negative one, since the latter is based only on the sample examined and

any particular specimen may fail to contain fungous elements which are present elsewhere. Furthermore, treatment may have decreased the amount of fungous material available.

The direct examination does not establish the identity of the species of fungus involved except in certain instances, which will be described later. The reason is that in the filamentous stage, which is usually observed, most fungi appear similar.

In most instances the direct examination of a specimen is facilitated by a procedure known as "clearing," by which most debris and host cells are converted into a translucent, homogenous mass in which cell outlines become indistinct, rendering the unaffected fungous elements clearly visible The specimen is thereby also softened so that it may be pressed out into a much thinner layer, which can be more easily examined For ordinary routine use we have not found anything better than a 10 per cent solution of potassium hydroxide. With more concentrated solutions crystallization may occur, obscuring the examination and at times presenting artefacts simulating fungi. Other solutions which have been advocated, such as xylene or a solution of sodium sulfite and chloral hydrate in acacia, present certain disadvantages.

Place the material to be examined on one end of a clean glass slide and add a small drop of a 10 per cent solution of potassium hydroxide. Put on a coverslip and add almost enough hydroxide to fill in the space between the coverslip and the slide. Pass the slide through the flame of a Bunsen burner three or four times until it shows bubbling, but avoid vigorous boiling. Press gently on the coverslip with a blunt object. Examine the preparation under the microscope. If it is not clear, reheat it and examine it again Repeat this procedure until the tissue is clear enough for satisfactory examination. The material is placed on one end of the slide so that the fingers are not burned when the slide is being heated, and the potassium hydroxide is added cautiously to avoid flooding.

As an alternative method if an immediate examination of the mount is unnecessary, the prepared slide may be left warming over a microscope lamp This prevents disorganization of the tissue to be examined. Care should be taken that evaporation does not cause crystallization. If the slide becomes dry, water should be added rather than more hydroxide so that the crystals will again dissolve.

There have been many modifications and additions to the above technique, most of which depend on staining the fungus elements in a distinctive manner While it is usually possible to dispense with such procedures, occasionally they may serve well in difficult cases A simple method recently described by Cohen utilizes a mixture of equal parts of 20 per cent potassium hydroxide and "Parker's Superchrome Blue Black Ink" ® as a substitute for the usual 10 per cent hydroxide solution. The periodic acid-Schiff stain (Hotchkiss-McManus) as recommended by Kligman and Mescon yields beautiful specimens but is too complicated for routine use

The use of lactophenol, as first described by Amann and later endorsed or modified by Langeron, Linder, Henrici, Swartz and Conant, and others, is one of the best methods of staining fungi in fresh tissue. The following formula is used:

Phenol crystals	20 Gm.
Lactic acid, syrup	20 Gm
Glycerin	40 Gm
Water	20 Gm
Cotton blue (C.B Poirrier)	0 05 Gm

The last ingredient is added after the other materials have been dissolved with gentle warming. The fresh tissue is first partially digested on a glass slide, a 10 per cent solution of potassium hydroxide being used. When sufficiently softened, the preparation is flooded with water, which is then removed by absorption with blotting paper. When the hydroxide has been entirely removed, the tissue is stained by the lactophenol solution and a coverslip applied. If desired, cement may be placed around the edges of the coverslip

When it is desired to hold for examination at a later time a slide prepared with 10 per cent potassium hydroxide, a drop of a 50 per cent aqueous solution of glycerin is placed at the edge of the coverslip. It will slowly mix with the hydroxide, producing a homogeneous mount which may preserve the specimen for several weeks or even months. Care must be taken that the coverslip is not disturbed. Such a method is useful when one does not at first find the material which should be present or if a thorough search must be delayed

Thin scales, such as those of tinea versicolor, erythrasma, or pityriasis capitis, may be placed on a slide, washed in acetone to remove fat, and mixed for three minutes with methylene blue, which is then drawn off with blotting paper The specimen is dehydrated with a 95 per cent concentration of alcohol and xylene and is mounted in Canada balsam. This method gives a permanent stained mount, but it is not suitable for thick sections Huber and Caplin use a preparation of polyvinyl alcohol, a plastic, for mounting thin tissue as well as for preserving material from cultures.

An aqueous solution containing 5 per cent potassium hydroxide and 25 per cent glycerin may be used when time can be allowed for clearing of the material, it offers a semipermanent specimen in which little or no crystallization occurs. When *actinomycosis or blastomycosis is suspected* [illegible] he pus

[illegible] 'arious Hyphomycetes which cause infections may be seen in the skin or its appendages either in the filamentous or in the arthrospore stage In the earliest phase of the infection the filamentous form is noted exclusively. Later, spores are observed, and in older infections they predominate.

In hairs, filaments are rarely noted except in those infected with T. schoenleini. Spores vary in size, being largest in the endothrix Trichophyta (T. violaceum, T. crateriforme, T. sulfureum). The hair shaft may be noticeably invaded when infection is due to these microorganisms and less so when it is due to one of the Microspora (such as M. canis or M. audouini). With the last-mentioned fungi, the spores are present in the sheath of Henle, external to the hair shaft. The position of the spores (whether they are external to or are invading the shaft) may be determined in a freshly made specimen, before the hair becomes too flattened, by moving the objective up and down.

The appearance of fungus-infected hair has been depicted in prior chapters. The predominant infections of hairs are caused by the three species of Microsporum. With these, small round spores in mosaic form are seen on the outside of the shaft of the hair. In other ectothrix infections (T mentagrophytes and T. rubrum), the spores are of medium size and occur in irregular groups, compact or loose, outside the hair shaft. We seldom see follicular infections due to ectothrix In the endothrix infections, the spores are usually seen in linear formation, since they are derived from the filamentous stage by segmentation. When the infection is due to T. schoenleini, the amount of fungus material is less than with other infections, and filaments, which may be irregularly segmented, are commonly observed. In addition, air bubbles are often present Because of this characteristic picture, favus may be recognized on microscopic examination.

In specimens from the glabrous skin, the fungus is usually present in the scales as filaments If the infection is of long duration, large numbers of spores may be noted It should be mentioned here that spores may be readily confused with artefacts, such as oil droplets

With tinea versicolor there are groups of spores (double-contoured) and numerous filaments which readily become segmented.

When scales from lesions of tinea cruris are removed and examined, filaments or spores in chains are seen. If the infecting microorganism is E floccosum, the elements are large The number of elements present in a specimen may vary, but with E floccosum the number is usually greater than with T rubrum or T mentagrophytes. C. albicans is revealed as clusters of blastospores in addition to nonseptated hyphae

The roofs of vesicles are good sources of fungus elements and often reveal septate mycelium or chains of spores in profusion It is in this tissue particularly that one is apt to note "mosaic fungi," the exact nature of which is as yet imperfectly understood (*see* section on artefacts).

In nail tissue one may observe hyphae similar to those noted in scales, macerated skin, or the roofs of vesicles These seldom branch, the elements are fairly homologous, and they are not seen in a tangled network Many spores may be present. After treatment, nail tissue may be the only available source of infected material in which fungi can still be demon-


A
B
E
F

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Fig. 114. Foreign material frequently found in skin scrapings. A, wool fiber. B, strand of cotton C, m[illegible]
lesion treate[illegible]
F, crystals c[illegible]
spores of Ly[illegible], an occasional ingredient in foot powder H, elastic fibers I, wood fiber and air bubble

strated. When the invasion of the nail is superficial, as it sometimes is with T. mentagrophytes (leukonychia trichophytica), a profusion of filaments will be observed in the white mat, which is in reality a pure colony of the fungus.

In nails invaded by C. albicans, when the marginal discolored and undermined tissue is examined, clusters of round cells in mosaic pattern are to be found. Filaments are rarely seen. Oil droplets must be differentiated from the yeastlike cells.

When material from the contents of superficial pustules or blebs is examined, fungi are rarely found Pus aspirated from deeper lesions or removed from a discharging sinus should be examined for the structures of one of the fungi which produce granulomas. Granules or noticeable small clumps of organisms may be quickly observed when a drop of fresh pus on a slide is covered with a coverslip. They usually denote an Actinomyces or Nocardia. S schenckii is difficult or impossible to demonstrate in direct preparations. The budding microorganism of Blastomyces and the spherules with endospores of Coccidioides may be observed. More detailed descriptions will be found in the section on the various deep mycoses.

The direct examination of sputum usually is not reliable, even if the specimen is centrifuged, since contamination is hard to eliminate. However, A bovis and C albicans are both recognizable in the forms in which they appear. Fungi are notorious as secondary invaders in pathologic tissue As such, they may also harm the host. Cultural studies followed by critical analysis and correlation with clinical facts are here doubly advisable. Dickson has shown that C. immitis is not uncommonly observed in the San Joaquin Valley of California in the sputum of patients who have a febrile pulmonary disorder. In searching for H capsulatum in blood, both stained and unstained mounts should be examined. The microorganism is usually found intracellularly.

Stained sections of pathologic specimens from lesions in the skin or in other organs may reveal fungi of many different species If one is trained only in observing the appearance of unstained slides, the staining characteristics and the shrinking of the specimen are apt to cause difficulty, and one may hesitate to make a definite diagnosis from a given slide. Structures such as those observed in blastomycosis, histoplasmosis, or coccidioidomycosis are characteristic even in stained preparations.

2. Dubious fungous forms and artefacts —The forms to be described will be observed fairly frequently, and their appearance should be readily learned

The "mosaic fungus" (Weidman) is an artefact in the opinion of the majority of those who have examined many scrapings Stumpf claimed that the mosaic fungus is made up of free fatty acids. Davidson and Gregory stated that it consists of cholesterol crystals, Cornbleet and his coworkers agreed with this observation on the basis of their experiments using fluorescence microscopy. Some still hold that it is a degenerate form

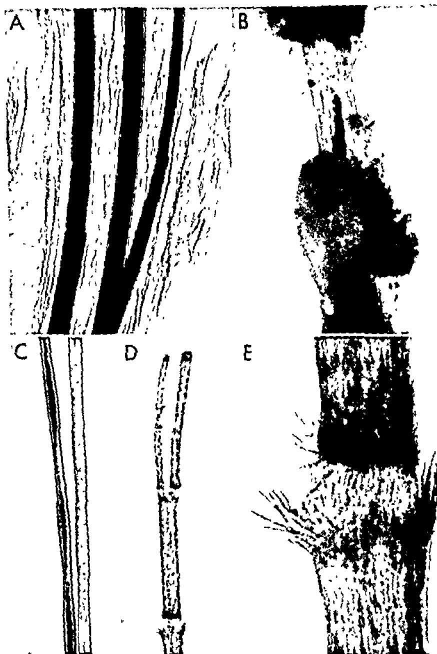


Fig. 115 Nonmycotic hairs. A, tinea amiantacea, × 56 B, lepothrix, × 108 C, monilethrix, × 56 D and E, trichorrhexis nodosa, × 52 and 230, respectively

of a pathogen. Dowding and Orr reviewed the literature and cited their own experiments as evidence that the mosaic fungus is transformed from T. mentagrophytes. They have observed (as we have) that ordinary hyphae and mosaic segments are occasionally to be seen in apposition; that normal spores and hyphae are sometimes part of the mosaic formation, and that the amount of mosaic material increases while the number of living fungi decreases during the healing of lesions In a later communication Dowding presented additional evidence that the mosaic structure originates from a dermatophyte, passes through the cell walls of the hypha, and later collects in the typical pattern. Getz and collaborators believed with Gotz that the mosaic fungus is a product of oxidation of fats in the epidermis.

The appearance of the mosaic form was described by Weidman as follows:

> The segments are irregularly shaped, and are separated from each other by narrower or broader, but definite spaces, they have a moth-eaten appearance, and their edges and corners are rounded off They do not have any organized internal structure, arthrospores are not visible within the segments But it is the arrangement of the mycelium that raises the question whether this is fungus —not so much that it occurs in smaller and larger patches, but that the mycelium ramifies and anastomoses around the individual epidermal cells in such a way as to suggest that air or other refractile matter had become imprisoned between the cells These hyphae vary in width, until finally one recognizes only threadlike filaments coursing between the cells It requires fine discrimination to come to the conclusion that these are fungus and not inert intercellular accumulations I have applied the term "mosaic" to this form because, following as they do the intercellular clefts, the hyphae come to surround smaller and larger polyhedral spaces, which collectively give the "pavement" effect

The remarkable fact that this form is seen only in locations and usually in lesions suggesting a fungous origin has not yet been satisfactorily explained In lesions equally inflammatory or in scaly conditions of the skin remote from the hands and feet, it is seldom isolated. In the scales of psoriasis, pityriasis rosea, or seborrheic dermatitis, the "mosaic" phenomenon is unknown. Thus it appears that the "mosaic fungus" may indicate a fungous infection without being itself a definite fungous structure

If the amount of vegetative fungous material is large, if there is branching, if there is a green or brown tone, or if the individual segments are large or of different sizes, one is fairly certain that the fungus is not a pathogen. Judicious selection of material after discarding the more superficial scales or nail tissue will usually obviate the necessity of deciding whether the fungus is a saprophyte or a pathogen In open lesions, particularly those of long duration, saprophytic fungi may colonize in the diseased tissue and will perhaps even produce some clinical symptoms

Oil and grease, air, hairs, cotton fibers, feathers, and many other substances may cause trouble for the novice One should mount specimens of various artefacts and become familiar with their appearance The variations in size of oil droplets or air bubbles stand out in contrast to the

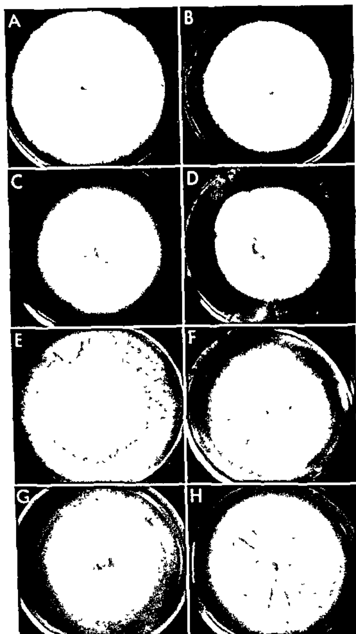


Fig 116 Comparison of cultural growths when different sugars were used Media on plates on left contained technical dextrose and those on right contained technical maltose A and B, T mentagrophytes, C and D, T rubrum, E and F, M canis, G and H, M audouini All growths are one month old

relative uniformity in size of fungous spores or yeast cells. With structures such as cotton fibers, examination of the ends will show a ragged or square effect, whereas a fungus filament is always rounded at its ends. Green and Shepard drew attention to the possible confusion with elastic fibers when the specimen is a shaving of skin extending into the cutis. Elastic fibers may even be observed in pus. The profusion of fibers, the absence of cross walls, the translucency, and the variability in size serve to differentiate them from fungi.

CULTURAL METHODS

When one wishes to determine the species of an infecting microorganism, it is necessary to study its appearance and behavior in culture on artificial media. Cultural methods are now extensively employed for the isolation of pathogenic fungi. The routine technique is not too difficult for the practicing physician. Throughout this book we have pointed out many times the obvious advantage of a precise diagnosis. The type of treatment may depend entirely on the cultural findings It is indisputable that the patient will nearly always benefit from the exact knowledge to be gained from cultural studies. Physicians are greatly indebted to Sabouraud, who established the pathogenic nature of many species of fungi He found that a culture medium which consisted of French maltose (imported from Germany), Chassaing peptone, and agar supported growth of most fungi when they were incubated at room temperature. He further demonstrated that there was a remarkable uniformity in the gross cultural appearance of any given species of fungus and that this was sufficient for its recognition in the majority of instances.

During World War I, maltose could not be obtained. The limited supply on hand was soon exhausted and substitutes were used, with varying success Weidman and McMillan showed that crude American dextrose was a satisfactory substitute for maltose Weidman and Spring found that 16 of 18 species of fungi which they tested produced satisfactory growths when Fairchild's peptone (an American product) was substituted for Chassaing peptone (a French product). Hodges also found Fairchild's peptone suitable for use Numerous synthetic media have been proposed; in theory, a medium in which the exact chemical constituents are known is to be desired Neither dextrose nor peptone is of constant composition, minor variations in the medium often result in changes in the characteristics of a fungous colony Weidman and Spring rightly stated that such a medium must prove its superiority over those now in use by being as differential as Sabouraud's test medium, internationally available and comprising ingredients which will not vary from year to year. For the present, the media listed in the following pages are recommended for routine use

It should be emphasized that only certain sugars are suitable for inclusion in the formulas of media Development of color in a colony or in the

(7) Autoclave for 20 minutes at a pressure of 15 pounds

(8) Slant and leave until the medium is solid.

The vast majority of mycologic work of the routine variety can be carried out with this one medium.

(b) *Modified dextrose agar.*—If the specimen to be cultured is removed from a grossly contaminated site, or if one has difficulty in obtaining a pure fungous colony, without coincident bacterial or mold growths, the addition of a selectively restraining antibiotic is advisable. Penicillin (20 units per cubic centimeter), streptomycin (40 units per cubic centimeter), and chlormycetin are effective against many species of bacteria. Chlormycetin is best, since it is heat stable, whereas the others are not The selective action of cycloheximide (actidione) against most of the air-borne molds has been studied by Georg. The growth of very few pathogenic fungi is restrained, the exceptions being Aspergillus fumigatus, Allescheria boydii, Nocardia asteroides, and some of the fungi considered of etiologic significance in maduromycosis.

The two agents chlormycetin, 0 125 mg. per cubic centimeter, and actidione, 0.5 mg. per cubic centimeter, may be added to the dextrose agar before autoclaving, as both are heat stable.

(c) *Dextrose broth.*—A liquid medium of simple structure may be useful in studying yeastlike fungi, to flood certain growths on a solid medium, or in the preparation of massive growths for use in making extracts

Dextrose (crude American)	40 Gm
Peptone (Difco)	10 Gm
Distilled water	1,000 cc

The method for making dextrose agar should be followed

(d) *Conservation agar* —This was advocated by Sabouraud to prevent loss of the character of the colony through excessive vegetative growth. Unless one is careful the colony may die because of slowness of growth on the conservation medium The method of making conservation medium is similar to that of the ordinary dextrose agar, the only difference being the omission of dextrose from the former.

Agar	18 Gm
Peptone (Difco)	10 Gm
Distilled water	1,000 cc

If desired, 20 Gm. of technical maltose may be included. The colony is then neither too luxuriant nor too scanty, and the characteristics of the culture remain constant

(e) *Cornmeal agar* —This is employed in the differentiation of various species of Candida (Monilia) and Cryptococcus It is also useful when one is studying the spore forms of the dermatophytes Its value is partly due to a minimal nutrient content, the growth, while scant, shows the characteristics of fructification.

adjacent medium may be an important feature of the fungus. We have found that the carbohydrate component of the medium is the fraction used by the fungus for this purpose; most monosaccharides can be utilized, but disaccharides, such as *maltose and lactose, and other complex sugars* cannot be used by fungi to form pigment.

Stock cultures may be kept on an ordinary medium until moderate growth has taken place and may then be stored in the refrigerator. To prevent contamination in handling and to lessen the drying of the agar, the top of the tube should be covered with cellophane kept on with a rubber band We have found cellophane better than tin foil or wax paper, as it is transparent and labels or crayon can be seen through it. In addition, cellophane is punctured less easily than tin foil when one is handling the tubes Under the conditions described, colonies may be kept for three to six months. For office practice, the small square half-ounce perfume bottles recommended by Wilson and Plunkett offer several advantages over test tubes or Petri dishes, although the latter will be needed for more detailed study in difficult instances.

The addition of yeast extract powder to a standard medium enhances the features of the fungus, such as the formation of spores, characteristic color, and contour. It seems to reduce the tendency for the organism to become pleomorphic. Georg and others have found the addition of thiamine hydrochloride especially helpful in the isolation of T. verrucosum.

1. FORMULAS.—The artificial media needed in routine work are not numerous The following kinds are useful.

(*a*) *Dextrose agar*.—This preparation is intended for routine use in the isolation of fungi. The only difference between this formula and that of Weidman's Pennsylvania medium is the substitution of Difco peptone for Fairchild's peptone and technical dextrose, or "syrupy glucose," for the crude American variety, both changes being without discernible sacrifice of any advantage.

Agar (granular)	18 Gm
Peptone (Difco)	10 Gm
Dextrose (technical)	40 Gm
Distilled water	1,000 cc

The pH is usually 5 8 to 6 2, although it is not usually necessary to be particular about this

(1) Add the agar to 700 cc of the water and soak for one hour

(2) Add the peptone and dextrose to the remaining 300 cc. of water Stir for a few minutes until both ingredients are dissolved.

(3) Cook the agar and water in an aluminum pot, stirring occasionally

(4) When the agar is almost dissolved, start to cook the peptone and dextrose mixture, stir

(5) When both the agar and the peptone and dextrose are dissolved, add the peptone and dextrose to the agar and stir

(6) Measure the mixture into test tubes or bottles.

Pork infusion solids	1 0 Gm.
Peptone (thio)	1 0 Gm
Sodium chloride	0 5 Gm
Sodium thioglycollate	0 1 Gm
Agar	0 05 Gm
Water q s a d	100 0 cc

To this basic formula may be added·

Methylene blue	0 0002 Gm
Dextrose	1 0 Gm.

The methylene blue is an indicator, the dextrose is for enrichment.

This medium may be obtained from Baltimore Biological Laboratory, 432 North Calvert Street, Baltimore.

2. Inoculation of Medium.—The area of skin from which material is to be taken is washed with 70 per cent alcohol. Then it is scraped with the blade of a sterile scalpel, and the material is transferred directly to the agar slant. The material is left on the surface when the scalpel is cut several times across the medium. We use this method for the culture of macerated skin, scales, nail tissue, material from a moist, exuding surface, and hair from the scalp. Hair can probably be best removed from the beard by epilating forceps. The scalpel scraped over the tongue gives one a good specimen from the mouth. Transferring the material immediately from the patient to the agar gives a high percentage of cultures free of contamination

A platinum loop of medium strength is useful in transferring specimens of serum, spinal fluid, bile, or sputum from specimen bottles Here it may again be emphasized that fresh material is desirable, since most normal and pathologic body fluids are good media for the incubation of fungi, and small foci of contaminants, which might be disregarded at first, are soon found in such massive quantities that they erroneously impress one as being of pathogenic titer.

Pus is transferred by means of a sterile syringe or a flamed platinum loop if the lesion is open. The material may be placed over a Bunsen burner after the cotton is taken out, before and after inoculation We have not found, however, that this procedure reduces the incidence of contamination, we have therefore discarded it as unnecessary and burdensome.

Care should be taken that the cotton plug is not contaminated while the inoculation is being made For instance, it must never be laid down It should not be withdrawn until the material is on the blade of the knife and is reinserted as soon as the inoculation has been completed

Contamination starting at the upper pole of the agar slant, away from the line of inoculation, or near the mouth of the tube or bottle usually has originated from the outside, from spores blown in while the preparation was open If contaminating organisms appear near or in the lines of inoculation, they have probably been carried into the tube along with the substance of the inoculum and thus probably were present on the patient

Yellow corn meal	40 Gm.
Agar	15 Gm.
Distilled water	1,000 cc

(1) Add the corn meal to 500 cc. of water and keep heated to 65 C for one hour. Filter through paper.

(2) Dissolve the agar in the remaining 500 cc of water by heating.

(3) Mix the corn meal and the agar

(4) Filter through cotton. This is a slow process, and the agar will cool and harden unless the flask is placed in a steam bath or sterilizer

(5) Measure the mixture into test tubes.

(6) Autoclave the tubes for 20 minutes at a pressure of 15 pounds

(7) Slant the tubes and leave them until the medium is solid

(*f*) *Potato-carrot agar.*—This agar is useful in demonstrating the color characteristics of a colony

Carrots	20 Gm
Potatoes	20 Gm
Agar	15 Gm
Distilled water	1,000 cc

(1) Wash and peel the vegetables and cut them into small pieces, then add them to 700 cc. of water and boil the mixture down to 500 cc. Filter through paper.

(2) Dissolve the agar in 500 cc. of water by heating.

(3) Mix the vegetables and the agar.

(4) Measure the mixture into test tubes.

(5) Autoclave the tubes for 20 minutes at a pressure of 15 pounds

(6) Slant the tubes and leave them until the medium is cooled

(*g*) *Littman oxgall agar (Difco)* —A selective agar, used by some for primary isolation, does not support the growth of many bacteria and molds. The appearance of pathogens on this agar makes their recognition difficult.

(*h*) *Wort agar (Difco)* —This commercial medium, with a pH of 4 8, is a good substrate for the isolation and differentiation of the yeasts and yeastlike organisms, as it almost eliminates the growth of bacterial contaminants This effect is due to the high hydrogen ion concentration, which, while not harmful to yeastlike fungi, inhibits the growth of bacteria

(*i*) *Wort agar enriched with fat* —A sufficient quantity of either extract of crude lanolin or butter is pipetted over the surface of freshly made wort agar and allowed to dry Benham recommended this agar for the isolation of Pityrosporum ovale

(*j*) *Chlamydospore agar (Difco)* —Being free of reducing agars, but containing a polysaccharide, this agar favors the formation of chlamydospores Its use is primarily in differentiating C albicans from nonpathogenic strains

(*k*) *Anaerobic medium (Brewer)* —This medium is used chiefly to isolate A. bovis

considerably. A colony may be flat, rounded, fissured, cerebriform, umbilicated, folded, or concentrically ringed. More than one feature may be present in the same colony. Changes in the composition of the medium may affect the gross appearance of a colony. The depth of the agar influences the appearance; this can be seen when a growth is present along the entire length of an agar slant where there is considerable variation in thickness. In general, the depth of agar required for mycologic specimens is greater than that used ordinarily in bacteriologic technique.

(*g*) The margin of the colony may be sharply defined or may fade into the medium.

(*h*) The texture of colonial growths of fungi varies a good deal. One observes a downy or filamentous growth when the vegetative aerial mycelium predominates and is loosely arranged. If the mycelium is closer together, the growth appears compact or velvety. A granular surface is due to the presence of spores. A pasty surface denotes a yeastlike microorganism, and a waxy appearance is characteristic of T. schoenleini

(*i*) The color both of the colony and of the medium is occasionally an important feature. A violet hue of the colony of T. violaceum is characteristic. The typical port-wi

until after two or three

side of the colony. A b

with many different fungi. Many fungi lose their colors after repeated subcultures. The character of the culture medium is important, since some media (like potato) will demonstrate pigment that ordinarily is not present.

(*j*) Submergence of the colony is seen in cultural growths of T schoenleini and of several other fungi Splitting of the medium (due to the wedge of growth) is not uncommon in old, compact growths

The same strain of fungus is subject to a range of variation in cultural appearance which may be due to temperature (season), moisture, or other factors. It is difficult to obtain a characteristic colony of T. violaceum or T tonsurans during the winter months In winter the early growth of different strains of T rubrum is fairly uniform, but in summer considerable variation in the gross cultural characteristics is common

(*k*) Pleomorphism may be a factor. After prolonged isolation on a culture medium, many fungi assume a vegetative character, as evidenced by a white fluffy growth almost always starting at the point of inoculation

M

a

eration, old age, or monomorphism, whichever it may be, is difficult to overcome once it has appeared Subculturing sometimes causes the microorganism to assume its original nature, but in such instances the growth is probably not truly pleomorphic It has been suggested by Sabouraud, Catanei, and others that this state may be present in a primary culture, thus the fluffy type of T mentagrophytes is considered by some to be a

To culture Actinomyces from material in which granules are present, add a large volume of saline and shake. The granules settle The supernatant fluid is drawn off. The granules are washed a second time and are then drawn up into a sterile pipet and transferred to the depth of the anaerobic medium

3. CHARACTERISTICS OF FUNGI ON CULTURE.—Species of fungi can usually be recognized by their cultural appearance. *With experience one* may recognize many species, as one would human acquaintances, without having to see all the features. At other times, particularly when variants appear, all the characteristics of the microorganism, both gross and microscopic, may be required in order to determine its nature.

It is well to examine the inoculated culture medium after two or three days (to see whether contaminating organisms are present), after five to seven days (for the early characteristics), and finally after 10 days to three weeks (for the characteristics of the full-grown prime colony).

4. ROUTINE EXAMINATION —(*a*) The date of inoculation should be placed on the label of the culture flask together with some means of identification. When the colony is examined, the age may then be readily determined.

(*b*) The kind of medium used should be noted. It may again be emphasized that even slight differences in the composition of the medium may alter the cultural appearance On growths sent to us for identification, we often find it necessary to transfer the culture to our own standard medium to develop the characteristics of the colony with which we are familiar

(*c*) The number of days before growth is first noted is significant.

(*d*) Rapidity of growth is indicative If a colony is at prime in seven to 10 days it may be considered a fast grower, if three weeks elapse before it can be recognized, it is a slow grower; most fungi are of intermediate character The rate of growth is influenced by many factors, such as temperature, the depth of the agar, and the type of culture medium In the summer the rate of growth of fungi is noticeably faster than it is during the winter months, the greater the depth of agar the faster and more luxuriant the growth, culture media containing dextrose or other nutrient substances support more vigorous colonies than starvation media without these substances.

(*e*) The luxuriance of growth is characteristic Fungi differ in their capacity to develop One fungus covers the entire surface of an agar slant within two weeks, another fungus, such as T schoenleini, never covers more than a small portion Weidman pointed out that there is a difference between volume and luxuriance of growth, although the two are usually seen together The factors which influence the rate of growth also affect the character of the colony

(*f*) Surface configuration aids diagnosis. The gross topographic characteristics of colonies (probably due in part to inequalities in growth) vary

considerably. A colony may be flat, rounded, fissured, cerebriform, umbilicated, folded, or concentrically ringed. More than one feature may be present in the same colony. Changes in the composition of the medium may affect the gross appearance of a colony. The depth of the agar influences the appearance; this can be seen when a growth is present along the entire length of an agar slant where there is considerable variation in thickness. In general, the depth of agar required for mycologic specimens is greater than that used ordinarily in bacteriologic technique.

(g) The margin of the colony may be sharply defined or may fade into the medium

(h) The texture of colonial growths of fungi varies a good deal. One observes a downy or filamentous growth when the vegetative aerial mycelium predominates and is loosely arranged. If the mycelium is closer together, the growth appears compact or velvety. A granular surface is due to the presence of spores. A pasty surface denotes a yeastlike microorganism, and a waxy appearance is characteristic of T. schoenleini.

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(k) Pleomorphism may be a factor After prolonged isolation on a culture medium, many fungi assume a vegetative character, as evidenced by a white fluffy growth almost always starting at the point of inoculation Within a short time the entire colony may be covered. Some fungi, such as M canis, develop this character after a short time, while other fungi, such as T violaceum, never assume the vegetative form This result of degeneration, old age, or monomorphism, whichever it may be, is difficult to overcome once it has appeared Subculturing sometimes causes the microorganism to assume its original nature, but in such instances the growth is probably not truly pleomorphic It has been suggested by Sabouraud, Catanei, and others that this state may be present in a primary culture, thus the fluffy type of T mentagrophytes is considered by some to be a

degenerate form of the granular type. We believe the two forms are variants. The development of pleomorphism may result in a loss of virulence, as evidenced by the degree of involvement of infected tissue. Catanei has performed experiments substantiating this observation.

5. Preservation of fungous colonies.—The span of time during which a fungus in culture is at prime varies somewhat with the species. In most cases it is short. Thus most pathogenic growths require two or more weeks to attain maturity and may be at their best for only a week or 10 days. In order to keep a display of fungi in culture and also to give students a representative collection of typical pathogens, use is made of some practical methods by which a fungous colony may be preserved in its typical form for an indefinite period.

If test tubes are being employed when the colony has acquired a characteristic appearance, the cotton pledget is moistened with 10 drops of a 40 per cent solution of formaldehyde and replaced in the test tube. After 24 hours the pledget is trimmed off even with the test tube and the entire end of the tube is dipped in paraffin to make a completely airtight seal The latter precaution is necessary to prevent evaporation of moisture from the agar, with resultant shriveling of the fungous growth. The gross appearance of the colony remains unchanged for many months This procedure eliminates all danger of accidental human inoculation, an important consideration with virulent fungi such as C. immitis. If bottles with screw caps are used it is only necessary to tighten the cap to secure preservation for several weeks. Dipping the capped end into melted paraffin will prolong this time indefinitely.

6 Culture mount —In order to identify species of fungi, it is often necessary to study the character of their spores and their arrangement. These are characteristically formed in the aerial portions of the colony. It is impracticable to study the entire colony directly under the microscope because of the density of the growth and because the margin of the colony, where it might be viewed, is entirely vegetative If portions of a colony are removed and mounted, there results great disruption in the arrangement of the material However, characteristic spore forms may often be demonstrated in this way If mounts are made from a subculture on cornmeal agar where the vegetative growth is reduced, the direct mount is more satisfactory A hanging-drop preparation, in which the fungus is grown in a drop of liquid medium in an enclosed space, has the disadvantage of a limited air supply, which modifies the growth so that the vegetative structures predominate With the two methods to be described, the first of which we owe to Henrici, the nature of spore forms may be satisfactorily studied The first is additionally valuable, since permanent stained mounts may be made

(*a*) *Coverslip method* —(1) Moistened filter paper or a damp blotter is placed on the bottom of a Petri dish and sterilized in an autoclave at a pressure of 15 pounds for 20 minutes

(2) Six coverslips are cleaned, flamed, and placed on the moist blotter or filter paper.

(3) A special medium is required. We use one containing 2 per cent dextrose, 0.5 per cent peptone, and 2 per cent agar. The medium must be filtered through paper to remove any foreign particles before sterilization. It is then melted, cooled to between 40 and 50 C., and inoculated with spores of the colony to be studied. It should be well shaken in order that a uniform suspension may be obtained.

(4) With a loop needle, a thin layer of the inoculated agar is spread over the surface of the coverslips.

(5) The organism is incubated at room temperature. When sufficient growth has taken place, the coverslips may be removed with flamed forceps.

(6) For immediate study and temporary preparations, the coverslip may be inverted on a drop of water on a slide and immediately examined.

(7) For a permanent mount, the air bubbles are removed by addition of alcohol (95 per cent). The alcohol is drained off and a drop of lactophenol is added with cotton blue. The coverslip is allowed to stand for two minutes and then inverted on a microscope slide. After two or three days, excess mounting medium is removed and the preparation is sealed with asphalt varnish

For alternative methods to improve the seal, (1) use the double coverslip method, with the lactophenol cotton-blue mixture between coverslips of dissimilar size, and after two to three days mount in Clarite, which does not turn yellow on standing; (2) allow the culture to dry, stain, and mount in Clarite.

(*b*) *Culture chamber method* —With this method, which is a modification of Henrici's culture chamber method, the aerial portion of the colony may be studied independently of the vegetative part.

(1) A thin layer of dextrose agar is poured into a sterile Petri dish and allowed to harden

(2) With a flamed hooked needle a hole is made through the agar, the cut portion being discarded. The hole may vary in size or shape but must be smaller than a coverslip.

(3) The pathogenic fungus to be studied is inoculated at three or four points on the rim of the hole

(4) A coverslip is placed over the hole, a small part being left uncovered to admit an adequate supply of air

(5) Progress of the growth can be determined by viewing the growth through the back of the Petri dish without opening the chamber. When the culture is sufficiently developed, the lid of the Petri dish is removed. This exposes the medium to outside contaminants, which may interfere with prolonged study

A method which advantageously combines features of the two above procedures was described by Riddell (1950)

(*c*) *Wet India ink preparation* —Weidman and Freeman called atten-

tion to the value of a wet India ink preparation in the differentiation of yeastlike growths They advocated the following technique: "A loopful of India ink is placed on a glass slide, and a loopful of the culture material is quickly emulsified in it. A large coverslip is quickly applied and pressed gently" Practice is necessary to bring out the halo effect (in Cryptococcus neoformans). Three precautions are essential. the preparation must be made quickly; the drop of fluid must be small; no previous mounting material, such as hydroxide, glycerin, alcohol, or stain, may be present.

(*d*) *Binding agents.*—(1) *Asphalt varnish This is a durable* agent, which does not chip After a long period there may be some separation Use while fresh. It may be obtained from any biologic supply house. (2) Duco cement. This is preferred by some. A seal is quickly attained. There is a tendency to brittleness, and adherence may not be as reliable as with other agents. (3) Clarite. This is a useful product which is preferred by many workers. (4) Polyvinyl alcohol. This may be mixed with phenol, lactic acid, and cotton blue. According to Huber and Caplin, it clears and dehydrates as well as providing a permanent hyaline mount.

7. HISTOLOGIC EXAMINATION OF CULTURES.—As an aid in the identification of a fungous growth, examination of the stained slide of a biopsy specimen of the culture may be helpful The best results are obtained when *the specimen is taken from the actively growing part of the colony in* the region of the periphery The slides are stained by the periodic acid-Schiff stain (Hotchkiss-McManus) The different species of fungi reveal a characteristic histologic picture as well as distinctive spores and vegetative findings These are further discussed under the various dermatophytes

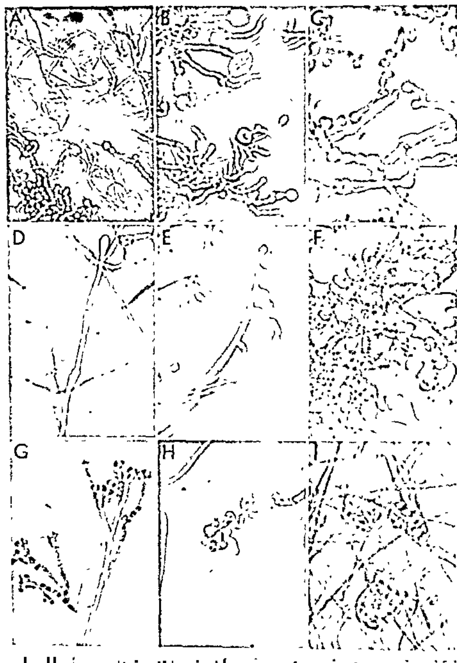
For purposes of description, the histologic sections may be divided into three parts

(*a*) The "fringe" is the surface of the colony Although essentially the site in which reproductive bodies develop, hyphae in small or large amounts are usually present. A "crust" or "shell" is often observed in the most superficial portion of the fringe. When lacking, this may have been dislodged during processing

(*b*) The "core" is immediately below the surface of the agar and made *up of varying amounts of a tangled mycelial net in which will be* seen a few spores

(*c*) The "substrate" is the remainder of the medium through which hyphae course to find nutriment Almost invariably the hyphae here are much finer than in the core

There are certain difficulties for the novice, both technical and interpretive The specimen must be removed with care not to dislodge the delicate surface, the optimum time to take it is when the colony is two to four weeks old, according to the species It may be difficult at first to orient the specimen The substrate may be identified in the somewhat opaque medium in which it resides when contrasted with the remainder of the slide It is often a challenge to recognize, from portions of the structure, such



I, nodular organs

distinctive forms as spirals, pectinate bodies, and fuseaux and to distinguish between the cross sections of hyphae and chlamydospores.

The method provides a means for preserving a permanent record of a colony. It is also promising as a basic means for investigation.

8. MICROSCOPIC CHARACTERISTICS OF DERMATOPHYTES.—When specimens of a fungous colony are examined, various vegetative and reproductive forms may be distinguished. Only vegetative forms are usually seen at the center or at the periphery of the colony; the spores (reproductive) are best located in the intermediary zone. These microscopic features are dissimilar in different genera, and frequently there are minor variations in species. The variations, however, may result from conditions of growth rather than arise as specific characteristics In most instances the gross appearance of a colony is sufficient to identify the microorganism provided the observer is familiar with the medium on which the fungus is growing. Confirmation of the cultural diagnosis is the chief purpose of the culture mount in routine practice.

(*a*) *Vegetative forms.*—(1) Mycelium, hyphae, and thallus. These terms indicate threadlike sterile organic material, which may be septate or nonseptate and may be present in large or small masses.

(2) Pectinate bodies. These are seen as "broken comb" unilateral projections This form is characteristic of M. audouini, T. schoenleini, and T. mentagrophytes.

(3) Racquet mycelium (mycelium *en raquette*) The hyphae show regular enlargement of one end of each segment. As a rule they are larger than other hyphae They can usually be seen in any species of Microsporum, in E. floccosum, and in T mentagrophytes

(4) Resorption of protoplasm The protoplasm constituting the contents of the mycelium may be irregularly distributed This characteristic is emphasized by staining the preparation.

(5) Nodular organ This is an enlargement consisting of closely twisted hyphae It may be formed by side branches twining around the main stem or by different filaments It is seen in M gypseum and T. mentagrophytes most frequently, and occasionally in other species.

(6) Favic chandeliers These forms, which resemble reindeer horns, are seen only in T schoenleini and are usually in profusion

(7) Spirals Corkscrew-like turns of mycelium are seen particularly in the older fluffy portions of T mentagrophytes They are more readily demonstrated on cornmeal agar than on dextrose agar

(8) Arthrospores A modification of the hyphae, with thickening of the walls in short segments, these forms may occur singly or in series.

(*b*) *Reproductive forms* —Reproduction occurs by asexual spores These are classed as macroconidia or as microconidia, according to size.

(1) Macroconidia (a) Fuseaux (pleuriseptate bundles, spindle spores) These are oat-shaped spores which may be connected with mycelium or may be free, since they are readily detached They may taper at both ends, as in M. canis, or one end may be blunt, as in E. floccosum. In some of the

Trichophyta they are usually observed while attached to mycelium. As a rule they are septate when fully developed; sometimes the partitions are incomplete if the specimen is immature. Some workers classify a dermatophyte according to the length of the fuseaux. It is our opinion that, in part at least, the length of the fuseaux may depend on the nutritional content of the medium.

(b) Chlamydospores. These large, thick-walled spores are observed along the course of a hypha, at its terminus, or on a lateral branch. They may be seen in most old growths, particularly in T. schoenleini or C. albicans, and in the old parts of the colony of E. floccosum. Evidence indicates that chlamydospores are of vegetative function and perhaps should more logically be considered with the preceding group (vegetative forms).

(2) Microconidia (aleurospores). (a) The small round or oval spores may be seen free, occurring singly or in grapelike clusters (*grappes*).

(b) The small spores may be seen in the substance of the mycelium and are then called arthrospores.

(c) If the spores are directly attached to mycelium or to short stocks, the resulting structures may be referred to as hyphae sporiferae (thyrsi sporiferi). Sometimes the mycelium bearing spores in this manner is of smaller caliber than sterile mycelium in the same field or from the same colony. These spores are the first formed and are to be found in specimens from the peripheral portions of a growth

ANIMAL INOCULATION

The inoculation of animals with material from patients for the purpose of diagnosis is seldom resorted to if a superficial infection is suspected Direct microscopic examination and a cultural study are preferable. For patients with a deep mycosis, a positive diagnosis may be difficult, in such instances the inoculation of animals susceptible to the infection may be advisable The kind of animal to be used will depend on the infecting microorganism, since there is variance in susceptibility Animal inoculation has also been used to determine pathogenicity when a new fungus has been isolated or when a fungus which is usually saprophytic has been under suspicion The results must here be interpreted with caution, as differences in susceptibilities of laboratory animals show that human beings may likewise respond in an individual manner At times, contaminating bacteria and fungi crowd out the pathogenic growth on the agar slant If the material is injected into a suitable laboratory animal, the pathogenic fungus may invade susceptible tissues and organs, from which it may be cultured in pure form When a fungus becomes pleomorphic, its original appearance can sometimes be restored by passage through a laboratory animal. Furthermore, the recovery and recognition of characteristic spore forms may be difficult from the cultural growth, whereas such forms may develop in laboratory animals

Guinea pigs, rats, mice, and rabbits are usually employed Cats (espe-

distinctive forms as spirals, pectinate bodies, and fuseaux and to distinguish between the cross sections of hyphae and chlamydospores.

The method provides a means for preserving a permanent record of a colony. It is also promising as a basic means for investigation.

8. MICROSCOPIC CHARACTERISTICS OF DERMATOPHYTES.—When specimens of a fungous colony are examined, various vegetative and reproductive forms may be distinguished. Only vegetative forms are usually seen at the center or at the periphery of the colony, the spores (reproductive) are best located in the intermediary zone. These microscopic features are dissimilar in different genera, and frequently there are minor variations in species. The variations, however, may result from conditions of growth rather than arise as specific characteristics. In most instances the gross appearance of a colony is sufficient to identify the microorganism provided the observer *is familiar with the medium on which the fungus is growing. Confirmation* of the cultural diagnosis is the chief purpose of the culture mount in routine practice.

(*a*) *Vegetative forms*.—(1) Mycelium, hyphae, and thallus. These terms indicate threadlike sterile organic material, which may be septate or nonseptate and may be present in large or small masses.

(2) Pectinate bodies. These are seen as "broken comb" unilateral projections. This form is characteristic of M. audouini, T. schoenleini, and T. mentagrophytes.

(3) Racquet mycelium (mycelium *en raquette*). The hyphae show regular enlargement of one end of each segment. As a rule they are larger than other hyphae. They can usually be seen in any species of Microsporum, in E. floccosum, and in T. mentagrophytes.

(4) Resorption of protoplasm. The protoplasm constituting the contents of the mycelium may be irregularly distributed. This characteristic is emphasized by staining the preparation.

(5) Nodular organ. This is an enlargement consisting of closely twisted hyphae. It may be formed by side branches twining around the main stem or by different filaments. It is seen in M. gypseum and T. mentagrophytes most frequently, and occasionally in other species.

(6) Favic chandeliers. These forms, which resemble reindeer horns, are seen only in T. schoenleini and are usually in profusion.

(7) Spirals. Corkscrew-like turns of mycelium are seen particularly in the older fluffy portions of T. mentagrophytes. They are more readily demonstrated on cornmeal agar than on dextrose agar.

(8) Arthrospores. A modification of the hyphae, with thickening of the walls in short segments, these forms may occur singly or in series.

(*b*) *Reproductive forms*.—Reproduction occurs by asexual spores. These are classed as macroconidia or as microconidia, according to size.

(1) Macroconidia. (a) Fuseaux (pleuriseptate bundles, spindle spores). These are oat-shaped spores which may be connected with mycelium or may be free, since they are readily detached. They may taper at both ends, as in M. canis, or one end may be blunt, as in E. floccosum. In some of the

stressed, they aid not only in establishing a diagnosis but in following the progress of the disease and in determining when cure has taken place. In certain cases of infection with M. audouini in which regrowth of hair is considerable, the diagnosis of tinea capitis may not be suspected In such instances, when only scaling of the scalp may be noted, fluorescence of the affected hairs is characteristic If the disease is unrecognized, children with



Fig 118 Hyphal fusion between two strains of identical species This does not occur when strains of dissimilar species are in proximity A, T mentagrophytes B, M audouini (*courtesy of late Dr Harold Orr and Dr Silver Keeping, Edmonton, Alberta, Canada*)

this condition constitute a serious menace, as they are potential foci for dissemination to other children

(*a*) In scalp infections due to M audouini and to M. canis the affected hairs appear as luminous, short, yellowish-green stubs Beare and Walker have recorded nonfluorescence in both infections but this must be an exceedingly rare occurrence, with scalp infections caused by M gypseum, fluorescence may or may not be noted

(*b*) Davidson and Gregory stated that hairs infected with T. schoenleini fluoresce like those infected with Microsporum and that hairs infected with other species of Trichophyton do not fluoresce We have noted that in infections due to T schoenleini the color is greenish but is usually less luminous than in infections due to Microsporum It is our experience that

cially kittens) may be used for cutaneous inoculation. In the first group, inoculations may be cutaneous, intraperitoneal, or testicular. The inoculum is usually a saline suspension freshly prepared from the cultural growth on dextrose agar or from finely ground fresh tissue. The animal is examined frequently for evidence of the infection. DeLamater and Benham described the course of the infection in animals successfully inoculated with a ringworm fungus. It is sufficient here to note that the response is confined to the epidermal structures of the animal. When a "take" occurs after inoculation of a species of fungus which causes a deep or systemic infection in human beings, a comparable infection is looked for in the experimental animal If it dies spontaneously, post-mortem examination will reveal the extent of the infection and something of its character. If the animal is still living six or eight weeks after the inoculation, it may be killed. According to Weidman, mice and rats are the animals of choice for testing pathogenicity of fungi. Practical advantages in using mice when possible (as with C immitis) are the facility of sterilization of the glass jar housing the mice, the ready collection of excreta, and rapid course of the infection

When difficulty is encountered in establishing a laboratory infection, resistance of the skin may sometimes be lowered by repeated inoculation of infective material into the same site

FUSION OF MYCELIUM

Fusion of mycelium was devised by Davidson and his co-workers to establish the identity of an unknown species. Only strains of the same species will fuse with each other when mycelia of two or more species are allowed to mingle The mycelia of two strains of M. canis fuse, but no fusion takes place between M. canis and M. audouini.

FILTERED ULTRAVIOLET RADIATION (WOOD'S LIGHT)

The use of filtered ultraviolet rays is important as an additional method of investigating some mycoses and of determining the causative species of fungus The "black light" has been the subject of extensive investigation, it is used in many different industries, where substances such as certain minerals show characteristic fluorescent properties Spurious currency, forged checks, and false covers over paintings may be revealed under the filtered rays when the true nature would not be readily detected in daylight. Margarot and Deveze first drew attention to the value of filtered ultraviolet rays as a diagnostic aid in infections of the scalp with Microsporum.

In dermatologic practice the important fluorescent effects noted when filtered ultraviolet rays are used as a sole source of radiation may help to detect pathologic conditions and to differentiate fungi in cultures

1. The value of the rays in cases of tinea capitis cannot be over-

That fungi in culture fluoresce was first noted by Margarot and Devèze. Vigne mentioned that T. tonsurans (T. crateriforme) shows a strong violet fluorescence in culture. Bommer pointed out that fungi in culture display a fluorescence different from that observed in the diseased hair and cited as an example the fact that whereas hairs infected with M. audouini have a green fluorescence, the culture shows a yellowish-brown tint with a light violet shimmer on the surface. He stated that in an examination of about 200 cultures of fungi on Sabouraud's medium he could not establish a variance in fluorescence corresponding to the cultural differences. Using a special medium containing urea and sucrose with the addition of minerals, the reaction of which was neutral, Mallinckrodt-Haupt and Carrie obtained differences in fluorescence among several species of fungi. It is interesting here to note that Cortese, in working with several species of Actinomycetes, was able to extract fluorescent material with weak alcohol, purifying it by shaking with acidified ether. The substance was found to be amorphous, odorless, and reddish brown It belonged to the group of porphyrins and showed a marked fluorescence in high dilutions. Robinson, Figge, and Bereston were able to exhibit fluorescent material from infected hair by boiling in distilled water. Bereston and Crosswhite and others have studied the fluorescent material by means of spectroscopy. The composition of the culture medium, in our experience, has little effect on the fluorescent coloration of a fungus The characteristic hues usually develop early in the life of a colony and may quickly fade or change The subject is further discussed under the individual fungous infections.

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hairs present in follicles invaded by ectothrix Trichophyta do not fluoresce. It is unwise, also, to depend on the fluorescence test in scalp infections caused by T. tonsurans. Sometimes the test is positive, but more frequently fluorescence cannot be demonstrated. However, with T. violaceum (endothrix), fluorescence of the infected hairs is a useful observation.

2. Animal carriers (particularly kittens) of certain pathogenic fungi may or may not be detected by fluorescence of affected hairs. When fluorescence is observed under filtered ultraviolet rays the appearance is identical with that of human hairs affected with the disease. However, it is the experience of Georg that only 32 per cent of infected kitten hairs fluoresce.

3. Tinea versicolor shows an individualistic color sufficient not only to establish the correct diagnosis but to determine the extent of the eruption, even when it has faded until its presence cannot be detected clinically. Other fungous eruptions involving the glabrous skin, the groin, or the feet, and the secondary eczematous and dyshidrotic eruptions of the hands and other parts, as well as infections with Candida and the deep fungous infections (sporotrichosis, actinomycosis, blastomycosis, coccidioidomycosis, and so on) do not fluoresce in any characteristic fashion when observed under filtered ultraviolet rays

4 Hairs affected by lepothrix fluoresce.

5 Keratin fluoresces, and when it is increased more luminosity may be seen The palm is brighter than the dorsum of the hand. Normal teeth and nails fluoresce brilliantly. The differentiation of certain diseases of the nails is aided. Warts and keratoses show a bright fluorescence, while molluscum bodies exhibit a dark center.

6 Some fading and indistinct eruptions become clearer when observed under filtered ultraviolet rays An accentuation of the syphilitic roseola is frequently apparent, and this finding is useful when the diagnosis is not easily made, particularly when concomitant findings are not present. Lentiginous and pigmented lesions usually appear darker when seen under filtered ultraviolet rays than when observed in ordinary light.

7. Many inorganic substances fluoresce When a drug such as salicylic acid or a product such as petrolatum is present on skin examined under filtered ultraviolet rays, the underlying condition may be masked Atabrine was observed by Bereston and Cohen to cause greenish fluorescence of scalp hair simulating the picture seen in tinea capitis

8 Various fungous growths in culture may be distinguished by their characteristic fluorescent colorations. We have studied this method of determining species of fungi for many years and can testify to its value and specificity The characteristic fluorescence of a fungus appears to be a most stable feature, resisting so-called pleomorphic changes. Variants of a species which appear totally unlike are recognized to be related by their appearance under the rays It seems to us that the method has been in use sufficiently long to have proved of merit and should be more widely employed.

40. Experimental Aspects

At first glance it must seem odd that medical mycology, being the oldest of the microbiologic sciences and antedating bacteriology by several decades, presents even today so many unsolved problems. While it is true that a high degree of complexity is the rule in mycologic studies, there is a much simpler reason for the lack of successful completion, in that comparatively they have not as yet been very intensively pursued. It must be granted that excellent mycologists have been functioning in all eras, but they have been pitifully few in number and almost always so poorly supported financially that they had to do even the most menial tasks themselves In search for the reason, it is not necessary to go beyond the fact that, while some fungous diseases are highly dangerous to life and some infect almost all persons at some time or other, none exhibits both of these characteristics. It is not surprising, therefore, that for a long time the terribly fatal bacterial scourges of mankind attracted the vast majority of those interested in microbiologic scientific investigation

In recent years, however, medical mycology has been receiving an ever-increasing share of attention, for the most part because so many of the previously attractive problems in other fields have been solved While some notable advances have occurred, many challenging puzzles lie ahead Many of the clinical manifestations of mycotic diseases are still poorly understood, and there is a discouraging lack of knowledge concerning their physiologic and immunologic aspects The life cycle of many pathogenic fungi is not fully known, nor are their requirements for survival, growth, and virulence Without a great deal of progress along these lines, spectacular successes are unlikely

Even today it is universally agreed that the therapy of most fungous diseases is distinctly unsatisfactory Only rarely has this realization stimulated definitive studies of the problems as a whole, on the contrary, thousands of communications deal only with attempts to achieve success by using chemicals which in vitro seem to possess fungicidal or fungistatic properties Of numerous medicaments intended to suppress the dermatomycoses (and all too frequently claimed to be able to do so) none can be

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COMMERCIAL SOURCES OF CULTURE MEDIA

1. "Difco" media of many kinds are available in bulk through firms selling laboratory

prepared

ed media

in 15-cc perfume bottles

and planning, lest he mislead his colleagues for some years by unreliable conclusions. The author should realize how difficult it is for him to be truly unbiased (especially if his investigation is supported financially by commercial firms who cannot be strictly disinterested) He should, also, be able to set for his studies sufficiently rigid controls so that he makes errors neither of omission nor of commission.

The reader is referred to the informative and most valuable article by Livingood on *Clinical Investigation in Dermatology.* The dicta recorded would be applicable to any field of medicine and certainly apply to medical mycology. The following suggestions are offered as a guide to those who wish to carry out a clinical investigation in this field.

1. Consider carefully the object of the investigation and decide whether it is worth the time, effort, and expense.

2. Are you equipped to do the work? If not, will you solicit help that will sufficiently complement your abilities and knowledge? Some of the most satisfying research lies in co-operative studies between clinicians and laboratory workers, statisticians, or epidemiologists.

3. Plan the project in detail For instance, if a new drug is to be administered, the safety precautions to be taken, the number and age range of patients in the study, the length of time of observation, and the criteria for estimating the results are among the items that may be arranged before a start is made

4. Provide for suitable controls Failure to appraise your work critically makes its conclusions about valueless. It is surprising how many times one is confronted with negligence in this particular According to Ross, only 27 per cent of 100 unrelated articles on therapy taken from five reputable medical journals show adequate controls The controls may be of the paired comparison type provided the lesions are bilateral and in the same stage of development The controls may be in sequence with the active medicament, but if so should precede and follow in different groups. It is always desirable for the observer to be unaware of which patients are receiving the placebo therapy. Needless to say the drug and the placebo should have a similar appearance

5. The crux of the entire investigation is the ability, training, and scrupulous honesty of the principal investigator All the work will be fruitless or misleading if the data are not interpreted correctly. It is therefore the most important requirement that all information obtained be evaluated critically. As Livingood stated well, "The habit of quantitative and statistical thought is essential in clinical research " Before submitting a paper for publication, one must determine that the number of patients was adequate for statistical significance

It would seem that research of both fundamental and clinical types is vital to further progress Not every one is competent to undertake an investigation However, it is probable that mere competency is not the standard by which the desirability of such work should be judged. Rather, the

said to have earned a place beside the "wonder drugs" now available in other fields of medicine, neither has any of the scores of compounds as yet achieved such status in the treatment of the deep mycoses.

It has been particularly discouraging to observe that the more closely a chemical or antibiotic has approached reliable fungicidal efficiency, the greater have been the incidence and severity of toxic reactions in the human beings on or in whom it has been used. It seems probable that the somewhat higher position among the natural forms of life which is occupied by the fungi makes them less susceptible to drugs than their simpler relatives and more likely to be harmed only by medicaments tending to be toxic also to higher animals and man.

It has become evident that no medicament yet devised can penetrate reliably the keratin of skin, hair, and nails as deeply as can pathogenic fungi. At best, medicaments can do no more than slow the rate of penetration of fungal elements into keratin and its predecessors enough to allow it to be exceeded by the rate at which such structures grow toward the surface (the "epidermal effluvial current"), thereby pushing the organisms away from the body to be eventually shed.

Scientific research in medical mycology can be divided into two phases, fundamental and clinical.

Fundamental investigation needs the talents of many types of scientists. Mycologists, chemists, physiologists, epidemiologists, and immunologists must be afforded the opportunity of frequent intercommunication and preferably of close alliance in approaching a problem, so that no one of them will exceed the limits of his capacity and render an unrealistic report.

As an example of laudable progress in this direction may be cited the work of Ajello and others showing that the soil is a reservoir from which there are constantly being acquired infections with M. gypseum and probably other pathogenic fungi, even as C. immitis and H. capsulatum are also known to be harbored in the soil The problem of animal reservoirs has been reviewed constructively by Georg Several competent mycologists have concerned themselves with detailed cultural studies which have brought two or more species of fungi into synonymy, usually thereby adding to the certainty in the minds of clinicians that the resulting diseases are identical clinically Such improvements in terminology are important, in spite of the fact that they are sometimes confusing to readers

It is possible to inoculate laboratory animals with some of the fungi pathogenic to man but not with others, so that investigations of the latter are doubly difficult

Clinical investigations are of the utmost importance but are unfortunately extensively underrated This judgment is undoubtedly deserved in considerable measure, because a large proportion of the reports are of little or no conclusive value. It is extremely difficult to carry out a definitive clinical evaluation of a method of therapy, for example, and one which should not be entered upon by any clinician without considerable thought

41. Contaminants

MOST physicians approaching the subject of medical mycology regard the study of the fungi usually classed as contaminants as an unnecessary nuisance The acquisition of a detailed knowledge of them requires, indeed, a lifetime of effort and obviously would be inappropriate. A small amount of information concerning them is absolutely indispensable, however, and can be easily acquired There are three reasons why the practitioner will benefit by such information

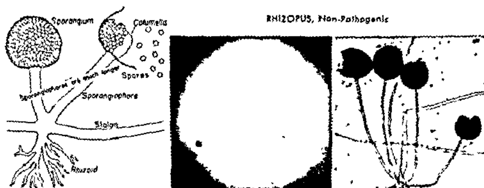
First, the spores of many fungi not pathogenic for man are so widely distributed over the globe as to deserve the adjective ubiquitous Thus the medical mycologist cannot possibly avoid finding them growing in his cultures, having arrived there either by being present in the inoculum obtained from the patient or by contamination from spores air-borne into the flask It is, of course, advisable to reduce contamination of both sorts to the lowest possible minimum, cleansing the diseased area thoroughly with 70 per cent alcohol before selecting the specimen will help minimize the former, while the use of culture flasks with the smallest possible openings may reduce the latter Even with the most nearly ideal technique, however, contamination will occur occasionally

Second, nonpathogenic fungi are by no means always easily recognizable as such, many species bear more or less resemblance in the gross appearance of their cultures to the fungi accepted as pathogens, and some are differentiated only with considerable difficulty The literature contains many instances of inaccurate classification Familiarity with the appearance under the microscope of the typical reproductive structures of

investigator's reputation for worth-while contributions will depend on his ability to criticize his own work and to be ruthless in discarding data which do not fulfill the requirements mentioned.

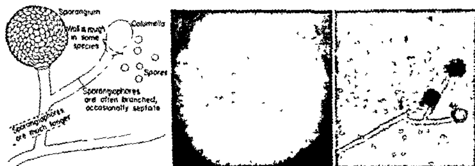
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spored, columella prominent, sporangial wall not cutinized, at maturity almost wholly disappearing, sporangiospores globose to oval or angular and dark. *Colony developing rapidly, soon covering the surface of the agar* and climbing up the sides of the Petri dish or test tube by means of the stolons

2 MUCOR —*Mycelium developed profusely both in and on the substratum*, lacking definite rhizoids and stolons, sporangiophores arising singly from the mycelium at any point, erect simple or branched, all branches terminating by large, globose, many-spored sporangia, sporangiospores globose to ellipsoid Large chlamydospores are frequently found in the mycelium or sporangiophores Colony develops rapidly, soon covering



MUCOR, Occasionally Pathogenic (Paronychia)

the surface of the substratum with a white cottony growth M racemosus is the commonest species and is of interest because it can ferment sugars and has been used successfully in producing industrial alcohol M paronychius was found to be the cause of paronychia among workers in the orange products *industry This organism occurred in nature as the cause* of a center rot of cull oranges

In general, nonpathogenic fungi tend to be bright-colored, brown, or black, while the majority of the pathogens are light-colored or white. Before discarding a brown or black colony as unimportant, however, one must consider Sporotrichum schenckii and, under appropriate circumstances, Phialophora verrucosa, Hormodendrum compactum and pedrosoi, Piedraia hortai, and species of Madurella. Before discarding a green or olive-colored specimen, one must eliminate from consideration *Epidermophyton floccosum*. A mucoid colony cannot be accurately classed as representing bacteria or a nonpathogenic yeast until careful search for the features of the pathogenic species of Candida or Cryptococcus has been made. On the other hand, a white fluffy growth does not necessarily indicate a pathogenic fungus, since many contaminants present this picture. A red-wine color diffusing into the agar does not signify the presence of Trichophyton rubrum; at least 10 other fungi may produce it.

We have found representatives of somewhat more than 50 genera of fungi as contaminants in medical mycologic cultures with sufficient frequency to deserve some attention. It is hoped that the following brief discussion and accompanying illustrations of the most commonly encountered contaminants will aid in their identification.

THE BREAD MOLDS

The fungi frequently referred to as bread molds are Phycomycetes and are members of the order Mucorales. They are characterized by a rapidly growing, profusely branched mycelium which when young is without cross walls but in age frequently becomes septate. The members of this group are saprophytic organisms found in soil and on decaying plant parts, especially fruits. In culture the mycelium is of two kinds, nutritive hyphae buried in the substratum and aerial hyphae from which sporangiophores bearing the reproductive structures arise. Asexual reproduction is accomplished by sporangiospores borne in large, globose to pyriform, many-spored sporangia. In development the sporangium becomes separated from the sporangiophore by the formation of a hemispherical columella protruding into the sporangium. Cleavage planes develop in all directions within the sporangium, finally cutting the protoplasm into small, usually uninucleated bits. These small protoplants round up, become surrounded by a cell wall, and become the sporangiospores The sporangial wall as a rule is thin and easily broken

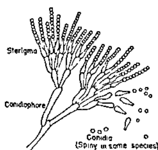
The species most frequently encountered as contaminants belong to two genera, Rhizopus and Mucor.

1. Rhizopus.—Sporangiophores fasciculate, arising from long arching stolons opposite the rhizoids, which are found at points of contact of the stolons with the substratum Sporangia terminal, large, globose, many

BLUE-GREEN MOLDS

The blue, green, yellow, brown, and black molds of the tribe Aspergilleae are among the most widely distributed of all fungi. They are of great economic importance in industry and as the causal organisms of food spoilage. Species occur on decaying organic matter everywhere from the arctic to the tropics. In culture the Aspergilleae produce rapidly growing colonies of various colors—blue, green, yellow, orange, brown, or black. The medium surrounding the colony is frequently colored. These molds are characterized and differentiated from other fungi by having highly specialized conidiophores from which the conidia arise in chains. The five genera usually included in this tribe are differentiated by the manner in which the conidia are produced.

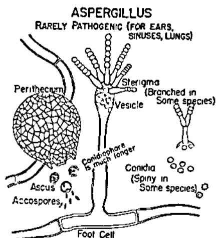
1. ASPERGILLUS —Thom and Raper (1945) recognized 78 species and many varieties of Aspergillus, and a few of these are almost ubiquitous. Colony growth is rapid but is too variable according to species for any typical description of the genus as a whole The conidiophores arise as erect hyphae from the vegetative mycelium The hyphal cell which branches to give rise to the conidiophore is called the foot cell. The apex of the conidiophore becomes swollen into a vesicle from which arise one or two rows of elongated bottle-shaped cells, the sterigmata The mature sterigmata bear chains of single-celled globose conidia. A. niger makes citric acid when growing in a glucose solution The colony shows many black pepper-like dots near the surface of a coarse woolly mat A flavus, a frequent cause of decaying fruit, shows greenish-yellow colonies with a coarsely granular surface. A. fumigatus, an important pathogen for birds, causes "brooder pneumonia" in newly hatched fowls. Pathogenicity for man occurs occasionally The colony is olivaceous-green and coarsely granular.

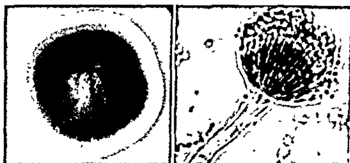




PENICILLIUM, Rarely Pathogenic (for ears, lungs)

2 PENICILLIUM —This genus, like Aspergillus, is distributed over the globe The gross appearance of the colonies is so variable that no type description can be made All show a powdery surface, various species ex-

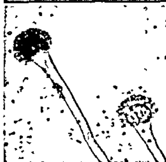

ASPERGILLUS
RARELY PATHOGENIC (FOR EARS, SINUSES, LUNGS)
Perithecium
Sterigma
(Branched in Some species)
Vesicle
Conidiophore is much longer
Conidia
(Spiny in Some species)
Ascus
Accospores
Foot Cell

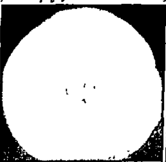








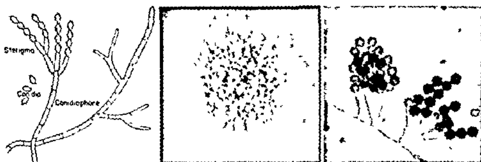






do not form chains but fuse with conidia from neighboring sterigmata to form clumps or balls held together by a gelatinous matrix.

5 SCOPULARIOPSIS —Scopulariopsis superficially resembles Penicillium, but the conidiophores are short and the penicillium is irregularly formed; the tubular sterigmata may often arise singly along the mycelium

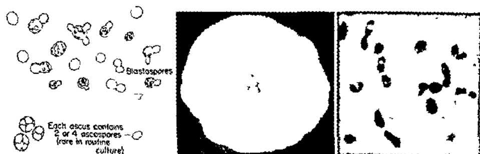


SCOPULARIOPSIS, Rarely Pathogenic (for ears, nails)

The rough-walled conidia are lemon-shaped, with a pointed apex and a truncate collar or connective at the base The conidia of Scopulariopsis are the only members of Aspergilleae which show a definite connective Species of Scopulariopsis cause decay in vegetables and dairy products Reports have been made of Scopulariopsis causing nail infection and deep-seated granulomatous lesions S brevicaulis is the species most frequently encountered, developing buff-brown colonies with a finely granular surface

YEAST AND YEASTLIKE CONTAMINANTS

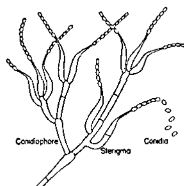
Yeast is a general term applied to unicellular colorless organisms reproducing by budding (blastospores) and characteristically forming pasty moist colonies The true yeasts are nonfilamentous single-celled budding fungi which at some time in their life history produce endospores (asco-



SACCHAROMYCES, Non-Pathogenic

hibit shades of green, pink, brown, yellow, or orange. The color is due to the numerous conidia. The conidiophores of Penicillium differ from those of Aspergillus in that they branch in a characteristic symmetric or asymmetric brushlike fashion. Sterigmata bearing long chains of globose conidia are found at the ends of the branches. P. glaucum and P. italicum are both common causes of fruit rot of oranges, apples, and peaches. The colonies of the former show yellow to white spots on a green background, while the latter is smoothly green.

3. PAECILOMYCES.—Paecilomyces is similar to Penicillium in having branched conidiophores but differs in that the branching is irregular and

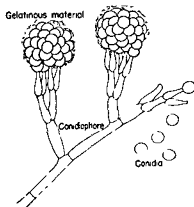




PAECILOMYCES, Non-Pathogenic

only in part verticillate The sterigmata are long and tubular and are widely bent away from the axis of the conidiophore The oval conidia are borne in long widely divergent chains giving rise to powdery colonies. At least one species has been reported to produce a bronchial pulmonary infection in man

4 GLIOCLADIUM —The conidiophores form a typical penicillus, as in Penicillium. The ovoid conidia when they are cut off from the sterigmata

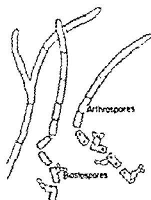


GLIOCLADIUM, Non-Pathogenic



the organisms are simple budding cells similar to Cryptococcus except for the presence of a carotinoid pigment. Ascospores are not produced

3. GEOTRICHUM.—Geotrichum produces a colony with a waxy moist surface and a thin disk of radiating gray or white moist mycelium The microscopic picture shows true mycelium which disarticulates into thin-walled rectangular cells (arthrospores); neither blastospores nor ascospores are produced Geotrichum is encountered frequently in specimens removed from the mouth or anogenital region The species G candida (Oospora lactis) is commonly found in sour milk, milk products, and sewage

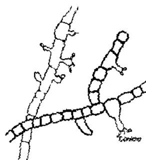




TRICHOSPORON, Non Pathogenic

4. TRICHOSPORON —Trichosporon is a common organism encountered in sputum specimens and frequently in skin scrapings It produces a gray-white or yellowish, heaped-up, rugose, waxy colony with a mycelial border and is easily confused with Candida or Geotrichum species Microscopic examination shows the true mycelium breaking up into arthrospores, which in turn bud, producing numerous blastospores

5. PULLULARIA —Pullularia is frequently encountered in sputum specimens and as an air-borne contaminant and in its early phases may be

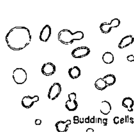




PULLULARIA, Non Pathogenic

spores) The false yeasts never produce endospores and may be unicellular budding organisms, as in Cryptococcus and Rhodotorula, or they may possess pseudomycelium or true mycelium, as in Candida. The other contaminant fungi which frequently produce moist yeastlike colonies resembling those of Candida are Geotrichum, Trichosporon, and Pullularia.

1. SACCHAROMYCES.—Species of Saccharomyces and Cryptococcus are prevalent in nature on ripening fruits and in soils and sewage and are frequently isolated as contaminants from skin. These two genera are iden-



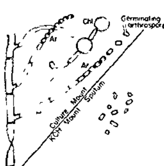
Does not form ascospores





RHODOTORULA, Non-Pathogenic

tified in culture by the production of colorless budding cells without mycelium. Species of Saccharomyces under proper conditions produce ascospores, Cryptococcus does not Saprophytic species of Cryptococcus may be distinguished from the pathogenic C neoformans by their inability







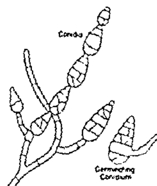
GEOTRICHUM, Rarely Pathogenic-Geotrichosis

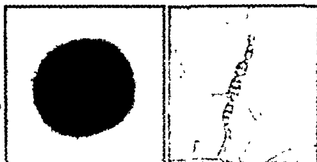
to grow at 37 C Species of Saccharomyces are commercially valuable in the fermentation of beer, wine, and the mash from which distilled liquor is made

2 RHODOTORULA —Two species of Rhodotorula, R glutinis and R mucilaginosa, occur rather commonly in cultures from vaginal smears, abscesses, and feces The colonies are creamy mucoid (occasionally rugose), showing various shades of pink, red, or orange Microscopically

lular conidia are olivaceous green to dark brown in color, are oval in shape, and are budded off from one another In old cultures two-celled conidia may be formed. H cladosporioides is the commonest species

2. Alternaria —Alternaria is probably the most commonly encountered genus among contaminant fungi Several species are almost ubiquitous and form dark olive-green or brown to black colonies which become

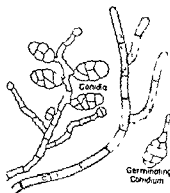




ALTERNARIA, Non Pathogenic

covered by a woolly light-colored mycelium in age The dark brown conidia are muriform, having both transverse and longitudinal cross walls, and are produced in chains from the apex of a short simple conidiophore Conidia are ovate with an alternative apex They are formed by budding from the one beneath by acropetal succession Any cell of the conidium may germinate and produce a germ tube

3. Stemphylium —Stemphylium produces colonies similar to Alternaria but usually black and without the aerial mycelium Conidiophores are frequently branched and bear single terminal conidia Conidia are





STEMPHYLIUM, Non Pathogenic

confused with C. albicans and S. schenckii. The colonies are at first yeastlike and pink or white, the center of the colony later becomes dark and eventually forms a heaped, wrinkled, black, shiny, leathery colony with a white fringe of submerged mycelium. Young mycelia are hyaline and thin walled, composed of short cells which give rise to oval hyaline conidia. These conidia frequently bud, producing the shiny yeastlike growth. The older mycelium often becomes thick walled and turns black and may break up into chlamydospores.

Candida, Geotrichum, Trichosporon, and Pullularia may be differentiated as follows:

Candida: mycelium or pseudomycelium present; reproduction by blastospores only.

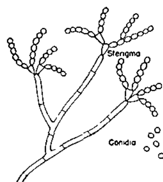
Geotrichum: mycelium disarticulating into rectangular thin-walled arthrospores; no blastospores.

Trichosporon. mycelium disarticulating into arthrospores, which in turn produce blastospores.

Pullularia. mycelium producing conidia, which in turn often bud, old mycelium often becoming black and forming thick-walled chlamydospores.

CONTAMINANTS WITH DARK MYCELIUM

Among the numerous fungi with dark mycelium which regularly form dark olive-green to brown or black colonies, three genera are most frequently encountered as laboratory contaminants. These fungi are all saprophytic or parasitic on vegetation and in soils. Their spores are more



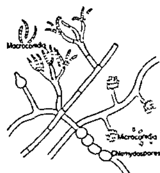


numerous in air than those of any other species and are frequently the cause of asthma or hay fever.

1. Hormodendrum —Hormodendrum species form rapidly growing colonies having a powdery surface Color of the colony varies with the different species from light to olivaceous green, dull gray, or dusky black Microscopic examination shows conidiophores of varying lengths bearing characteristic treelike clusters of conidia in branching chains The unicel-

often finely warted or reticulated and wrinkled Colonies of Epicoccum are fast growing and range in color from yellow to orange, red, or brown. Nonsporulating cultures are easily confused with those of Microsporum lanosum This fungus, while prevalent in the West, is apparently rarely seen in the East or Middle West

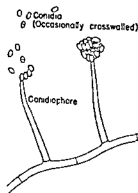
2. FUSARIUM.—Fusarium species are abundant in nature as plant parasites and soil saprophytes. Air-borne spores are numerous, arising from decaying vegetation and soil In culture, growth is rapid, producing cottony



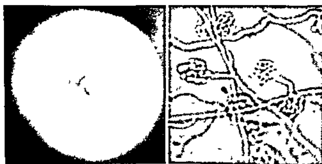
FUSARIUM, Non Pathogenic



colonies which have abundant aerial mycelium and are colored white, gray-tan, pink, violet, or red Several species display red or violet pigment diffused into the medium which has caused confusion with species of Trichophyton. F. oxysporum has frequently been incorrectly called Trichophyton rosaceum F. moniliforme also has been confused with T. rubrum. The uninitiated are further confused by the fact that Fusarium produces both microconidia and macroconidia Microconidia are unicellular, pro-



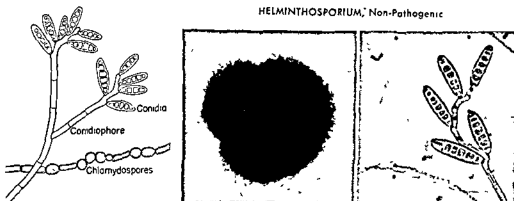
CEPHALOSPORIUM, Rarely Pathogenic-Maduromycosis



duced singly at the ends of short conidiophores, where they cling together in a ball held by a mucilaginous material Macroconidia are multicellular, curved, sickle shaped, or banana shaped, and are borne in clusters on

muriform, oval or packet-shaped, not attenuated as in Alternaria, and often verrucose.

4. HELMINTHOSPORIUM.—Species of Helminthosporium are found in nature as parasites and saprophytes on grasses. Conidia are found in large numbers in house dust and frequently cause an allergic reaction among

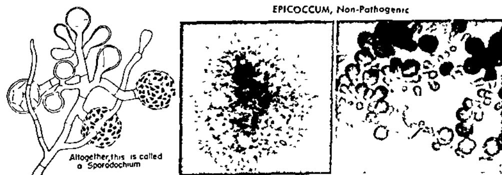


HELMINTHOSPORIUM, Non-Pathogenic

susceptible persons The colony is at first grayish, with a velvety, matted, surface, and later becomes green-brown to black, with a lighter-colored and often raised periphery. The conidiophores arise as upright branches from the mycelium and become bent or geniculate below the apex. Conidia are borne laterally on small geniculations on the bent-over apex. The multiseptate, cigar-shaped, thick-walled, straight or slightly bent spores are dark brown, olivaceous, or black, with the end cells often lighter in color. The *conidia have been confused with those of Microsporum*

FUNGI LESS FREQUENTLY ENCOUNTERED

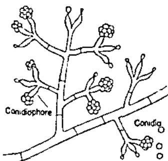
1 EPICOCCUM —The dark globose or ellipsoid multicellular conidia are produced singly at the upper tips of conidiophores which arise in a cluster (sporodochium) from the vegetative mycelium. The conidia are



EPICOCCUM, Non-Pathogenic

ing fungi encountered, and the cobweb-like growth soon fills the Petri dish or test tube and may even grow to the outside. Clumps or masses of orange or pink spores give the colony a characteristic color and appearance. Cylindrical or ovate one-celled conidia are produced abundantly This fungus is found in soil and on vegetation and is important as a contaminant in bakeries, causing the pink mold of bread and cakes The ease with which the conidia are dispersed makes it the most troublesome laboratory contaminant.

6 TRICHODERMA.—Species of Trichoderma are found as saprophytes on wood and soil, other fungi, and any material containing cellulose. In culture in the early stages, growth of white aerial mycelium is abundant

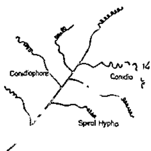


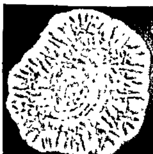



TRICHODERMA, Non-Pathogenic

After a few days, however, green spots appear near the periphery of the colony and the whole surface soon becomes green owing to the formation of clusters of conidia The conidia are formed singly but cling together in clusters at the tips of many-branched conidiophores. The branches are usually in groups of three.

7. STREPTOMYCES —Streptomyces contributes many species from soil, its typical habitat. It is difficult to differentiate the species and is usually not necessary In culture they all reveal themselves by a characteristic



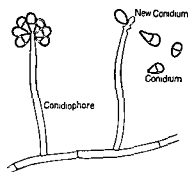


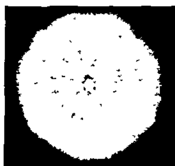

STREPTOMYCES, Non Pathogenic

branched conidiophores. The surface and embedded mycelium produce abundant globose chlamydospores.

3. CEPHALOSPORIUM.—Cephalosporium occurs as an air-borne contaminant from soil and produces white, tan, or pink colonies. The young colonies often have a moist surface and may be easily confused with young colonies of pathogenic fungi. The conidia are produced singly at the ends of short conidiophores and hang together to form gelatinous balls. Cephalosporium is indistinguishable from the microconidial stage of Fusarium, and the two genera are often confused.

4. TRICHOTHECIUM.—Trichothecium roseum, often called (Cephalothecium roseum), the only species known, grows rapidly in culture, producing a colony which is at first white and woolly and later becomes pink







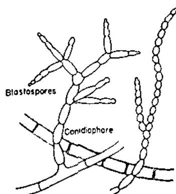
TRICHOTHECIUM, Non Pathogenic

or buff with a powdery surface. It is commonly known as the pink rot of apples and peaches and is readily identified by its clusters of two-celled conidia found at

5. MONILIA -

perfect stage, is

narily encountered in the laboratory. This is one of the most rapidly grow-



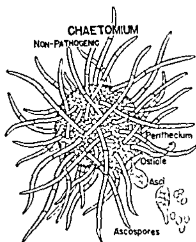
MONILIA, Non-Pathogenic

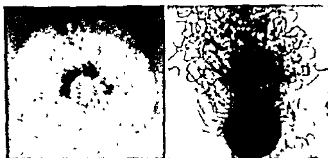




warted, and borne on short simple or clustered branches. The conidia have the same characteristics as those of Histoplasma capsulatum

10. CHAETOMIUM.—Chaetomium is encountered frequently as an airborne contaminant. In nature, species of Chaetomium are found in soil and as mildews on awnings, moist fabrics, leather, and moist paper. In



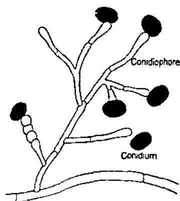


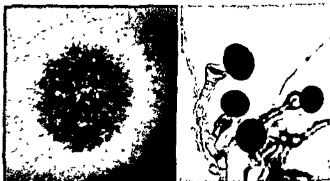
culture the growth is at first scant and olivaceous, later becoming brown or black and fluffy. Superficial ascocarps (perithecia) are produced on the surface of the colony. The perithecia are broadly ovate or ellipsoid and thickly and evenly clothed with slender, flexuous hairs The asci are clavate and evanescent Ascospores are single celled, lemon-shaped and smoky to dark brown in color.

11. CHAETOCONIDIUM.—Chaetoconidium is not very common but should be considered, because of its habit of slow growth and white to slightly buff colony it is easily confused with the dermatophytes The white fluffy mycelium remains sterile for a long time but eventually produces yellow-brown conidia on the surface The conidia (chlamydospores) are

odor, exactly that of a newly-dug grave or of a damp cellar. Colonies grow slowly, becoming heaped up and granular, and exist in many colors. The medium frequently becomes tinted with diffused colors of various hues. The mycelium is very fine and much branched and does not tend to break up into arthrospores. Oval or globose conidia are produced in long, often curled, chains from short side branches of the fine mycelium. *S. griseus* and *S. venezuelae* have become famous as the source of streptomycin and chloramphenicol (Chloromycetin). *S. fradiae* yields neomycin; *S. rimosus* produces oxytetracycline (Terramycin).

8. NIGROSPORA.—Nigrospora is frequently encountered in cultures from scalp scrapings. The growth is at first fluffy and dirty-white, rapidly

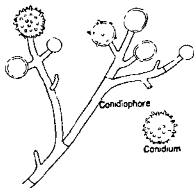


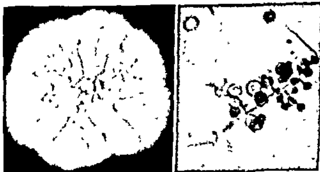


NIGROSPORA, Non-Pathogenic

covering the surface of the medium, when it is older, black spots of conidia appear. The conidia are jet-black, subglobose, and smooth, borne on inflated tips of branched conidiophores.

9. SEPEDONIUM.—Sepedonium is occasionally seen as an air-borne contaminant from soil. It produces a white fluffy colony easily confused with many of the pathogenic fungi. Conidia are globose, thick-walled,





SEPEDONIUM, Non-Pathogenic

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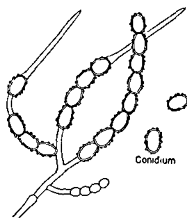
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found intercalary, either singly or in chains, on lateral branches. They are oval or spherical with thick verrucose walls. The fertile branches beyond the spore chain end in a long attenuated hyaline sterile tip

Index

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